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Endometrial injury in women undergoing in vitro fertilisation (IVF) (Review)

Lensen SF, Armstrong S, Gibreel A, Nastri CO, Raine-Fenning N, Martins WP

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[Intervention Review]

Endometrial injury in women undergoing in vitro fertilisation (IVF)

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ABSTRACT

Background

Implantation of an embryo within the endometrial cavity is a critical step in the process of in vitro fertilisation (IVF). Previous research has suggested that endometrial injury (also known as endometrial scratching), defined as intentional damage to the endometrium, can increase the chance of pregnancy in women undergoing IVF.

Objectives

To assess the effectiveness and safety of endometrial injury performed before embryo transfer in women undergoing in vitro fertilisation (IVF) including intracytoplasmic sperm injection (ICSI) and frozen embryo transfer.

Search methods

In June 2020 we searched the Cochrane Gynaecology and Fertility Group Specialised Register, CENTRAL, MEDLINE, Embase, CINAHL, LILACS, DARE and two trial registries. We also checked the reference sections of relevant studies and contacted experts in the field for any additional trials.

Selection criteria

Randomised controlled trials comparing intentional endometrial injury before embryo transfer in women undergoing IVF, versus no intervention or a sham procedure.

Data collection and analysis

We used standard methodological procedures recommended by Cochrane. Two independent review authors screened studies, evaluated risk of bias and assessed the certainty of the evidence by using GRADE (Grading of Recommendation, Assessment, Development and Evaluation) criteria. We contacted and corresponded with study investigators as required. Due to the high risk of bias associated with many of the studies, the primary analyses of all review outcomes were restricted to studies at a low risk of bias for selection bias and other bias. Sensitivity analysis was then performed including all studies. The primary review outcomes were live birth and miscarriage.

Main results

Endometrial injury versus control (no procedure or a sham procedure)

A total of 37 studies (8786 women) were included in this comparison. Most studies performed endometrial injury by pipelle biopsy in the luteal phase of the cycle before the IVF cycle. The primary analysis was restricted to studies at low risk of bias, and included eight studies. The effect of endometrial injury on live birth is unclear as the result is consistent with no effect, or a small reduction, or an improvement

(odds ratio (OR) 1.12, 95% confidence interval (CI) 0.98 to 1.28; participants = 4402; studies = 8; I^2 = 15%, moderate-certainty evidence). This suggests that if the chance of live birth with IVF is usually 27%, then the chance when using endometrial injury would be somewhere between < 27% and 32%.

Similarly, the effect of endometrial injury on clinical pregnancy is unclear (OR 1.08, 95% CI 0.95 to 1.23; participants = 4402; studies = 8; I^2 = 0%, moderate-certainty evidence). This suggests that if the chance of clinical pregnancy from IVF is normally 32%, then the chance when using endometrial injury before IVF is between 31% and 37%. When all studies were included in the sensitivity analysis, we were unable to conduct meta-analysis for the outcomes of live birth and clinical pregnancy due to high risk of bias and statistical heterogeneity.

Endometrial injury probably results in little to no difference in chance of miscarriage (OR 0.88, 95% CI 0.68 to 1.13; participants = 4402; studies = 8; I^2 = 0%, moderate-certainty evidence), and this result was similar in the sensitivity analysis that included all studies. The result suggests that if the chance of miscarriage with IVF is usually 6.0%, then when using endometrial injury it would be somewhere between 4.2% and 6.8%.

Endometrial injury was associated with mild to moderate pain (approximately 4 out of 10), and was generally associated with some minimal bleeding.

The evidence was downgraded for imprecision due to wide confidence intervals and therefore all primary analyses were graded as moderate certainty.

Higher versus lower degree of injury

Only one small study was included in this comparison (participants = 129), which compared endometrial injury using two different instruments in the cycle prior to the IVF cycle: a pipelle catheter and a Shepard catheter. This trial was excluded from the primary analysis due to risk of bias. In the sensitivity analysis, all outcomes reported for this study were graded as very-low certainty due to risk of bias, and as such we were not able to interpret the study results.

Authors' conclusions

The effect of endometrial injury on live birth and clinical pregnancy among women undergoing IVF is unclear. The results of the meta-analyses are consistent with an increased chance, no effect and a small reduction in these outcomes. We are therefore uncertain whether endometrial injury improves the chance of live birth or clinical pregnancy in women undergoing IVF. Endometrial injury does not appear to affect the chance of miscarriage. It is a somewhat painful procedure associated with a small amount of bleeding. In conclusion, current evidence does not support the routine use of endometrial injury for women undergoing IVF.

PLAIN LANGUAGE SUMMARY

Endometrial injury in women undergoing in vitro fertilisation (IVF)

Review question

To assess whether it is safe and effective to perform endometrial injury (also known as endometrial scratching), in women undergoing in vitro fertilisation (IVF), including intracytoplasmic sperm injection (ICSI) and frozen embryo transfer.

Background

Couples who have trouble getting pregnant may seek fertility treatments to help them conceive, such as IVF. In an IVF cycle, eggs are collected from the woman and are combined with sperm in the laboratory to create embryos. Embryos are transferred into the womb in the hope that they will implant and establish a pregnancy. Implantation is the process by which an embryo embeds itself into the lining of the womb; it is the first step toward establishing a successful pregnancy. It has been suggested that the chances of implantation are increased if endometrial injury is performed before replacement of the embryo into the womb.

Study characteristics

We included 38 clinical trials (8915 women) which had tested the effects of endometrial injury on the outcomes of IVF. The studies were conducted in different populations of women, and the way the endometrial injury was conducted also differed between studies in terms of the instrument used and the timing of the procedure in relation to the IVF cycle. Many of the studies were poor quality and at high risk of bias, and therefore we performed the main analyses only including studies that were not at high risk of bias. Of the 38 included studies, only eight were included in the primary analyses.

Key results

It is unclear whether endometrial injury affects the chance having a baby from IVF. The results suggest that, if the chance of having a baby from IVF is usually about 27%, then the chance of having a baby when using endometrial injury before IVF would be somewhere between

less than 27% and 32%. Similarly, for the outcome of pregnancy, if the chance of getting pregnant from IVF is assumed to be about 32%, then the chance of pregnancy when using endometrial injury before IVF is somewhere between 31% and 37%.

Endometrial injury does not appear to affect the chance of having a miscarriage from IVF. The endometrial injury procedure causes mild to moderate pain and a small amount of vaginal bleeding, although this is short-lived. This evidence does not support the routine use of endometrial injury for women undergoing IVF.

One small study compared endometrial injury using two different instruments in the cycle prior to the IVF cycle. All outcomes reported for this study were graded as very-low certainty due to risk of bias, and as such we were not able to interpret the study results.

Certainty of the evidence

For the primary analyses, the evidence is of moderate certainty. The evidence was reduced because the results were imprecise, and consistent with endometrial injury having no effect, being beneficial, and being harmful to the chance of getting pregnant or having a baby.

SUMMARY OF FINDINGS

Summary of findings 1. Endometrial injury compared to control in women undergoing assisted reproductive techniques

Endometrial injury compared to control in women undergoing assisted reproductive techniques

Patient or population: women undergoing assisted reproductive techniques
Setting: clinic
Intervention: endometrial injury
Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with Endometrial injury				
Live birth per woman randomised (studies at low risk of selection bias and other bias)	273 per 1,000	296 per 1,000 (269 to 324)	OR 1.12 (0.98 to 1.28)	4402 (8 RCTs)	⊕⊕⊕⊖ MODERATE [1]	
Live birth per woman randomised: sensitivity analysis (no high risk)	254 per 1,000	278 per 1,000 (177 to 409)	OR 1.13 (0.63 to 2.03)	229 (1 RCT)	⊕⊕⊖⊖ LOW [2 3]	
Live birth per woman randomised: sensitivity analysis (including all studies)	Meta-analysis not undertaken		-	7792 (29 RCTs)	⊕⊖⊖⊖ VERY LOW [4 5]	
Miscarriage per woman randomised (studies at low risk of selection bias and other bias)	60 per 1,000	53 per 1,000 (42 to 68)	OR 0.88 (0.68 to 1.13)	4402 (8 RCTs)	⊕⊕⊕⊖ MODERATE [1]	
Miscarriage per woman randomised: sensitivity analysis (no high risk)	53 per 1,000	61 per 1,000 (21 to 166)	OR 1.17 (0.38 to 3.58)	229 (1 RCT)	⊕⊕⊖⊖ LOW [2 3]	
Miscarriage per woman randomised: sensitivity analysis (including all studies)	54 per 1,000	56 per 1,000 (46 to 67)	OR 1.03 (0.85 to 1.25)	8092 (30 RCTs)	⊕⊕⊖⊖ LOW [4]	
Clinical pregnancy per woman randomised (studies at low risk of selection bias and other bias)	323 per 1,000	340 per 1,000 (312 to 370)	OR 1.08 (0.95 to 1.23)	4402 (8 RCTs)	⊕⊕⊕⊖ MODERATE [1]	
Clinical pregnancy per woman randomised: sensitivity analysis (no high-risk)	307 per 1,000	339 per 1,000 (229 to 472)	OR 1.16 (0.67 to 2.02)	229 (1 RCT)	⊕⊕⊖⊖ LOW [2 3]	
Clinical pregnancy per woman randomised: sensitivity analysis (including all studies)	Meta-analysis not undertaken		-	8786 (37 RCTs)	⊕⊖⊖⊖ VERY LOW [4 5]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Downgraded once for imprecision as the confidence intervals include appreciable benefit, no effect and harm
[2] Downgraded once for indirectness as the trial was undertaken in women undergoing frozen embryo transfer cycles only
[3] Downgraded once for imprecision as only one trial included and the confidence interval is wide
[4] Downgraded twice for high risk of bias as the majority of included studies display very serious risk of bias
[5] Downgraded once for inconsistency due to high statistical heterogeneity

Summary of findings 2. Higher compared to lower degree of injury in women undergoing assisted reproductive techniques

Higher compared to lower degree of injury in women undergoing assisted reproductive techniques

Patient or population: women undergoing assisted reproductive techniques
Setting: clinic
Intervention: higher
Comparison: lower degree of injury

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with lower degree of injury	Risk with Higher			
Live birth per woman randomised: sensitivity analysis (including all studies)	56 per 1,000	70 per 1,000 (18 to 240)	OR 1.28 (0.31 to 5.37)	129 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1 2 3]
Miscarriage per woman randomised: sensitivity analysis (including all studies)	56 per 1,000	70 per 1,000 (18 to 240)	OR 1.28 (0.31 to 5.37)	129 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1 2 3]
Clinical pregnancy per woman randomised: sensitivity analysis (including all studies)	111 per 1,000	141 per 1,000 (54 to 318)	OR 1.31 (0.46 to 3.73)	129 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1 2 3]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval;**OR:** Odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate:;the true effect is likely to be substantially different from the estimate of effect.

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[1] Downgraded twice for high risk of bias as the included study is associated with very serious risk of bias
[2] Downgraded once for indirectness as the trial is unlikely to be generalisable to other settings; for instance it compared pipelle with Shepard catheter and did not evaluate other types of endometrial injury
[3] Downgraded once for imprecision as only one trial is included and the confidence interval is wide

BACKGROUND

Description of the condition

Assisted reproductive techniques (ART) include treatments and procedures requiring in vitro handling of human oocytes and sperm, or of embryos, with the objective of achieving pregnancy and live birth. The most common forms of ART include in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI). We use the term 'IVF' to refer to IVF, ICSI and frozen embryo transfer. IVF is a widely used treatment for infertility, but success rates remain relatively low, with less than 30% of treatment cycles resulting in a live birth (Gunby 2010). A key determinant of treatment success is implantation of the embryo, which depends on two factors: the quality of the embryo and the receptivity of the endometrium. Even when good-quality embryos are transferred, implantation may not occur. The cumulative chance of achieving a pregnancy improves with second and third attempts, but thereafter the incremental improvement per additional cycle is reduced (Luke 2012). Recurrent implantation failure (RIF) is a clinical situation with many definitions; most published articles define RIF as failure of two to six previous treatment cycles (Polanski 2014). Implantation is a complex process, which is thought to be due in part to endometrial receptivity. One intervention suggested to improve endometrial receptivity is physical injury to the endometrium, also known as endometrial injury or endometrial scratching.

Description of the intervention

Endometrial injury, also known as endometrial scratching, is defined as intentional damage to the endometrium performed with the objective of improving the reproductive outcomes of women or couples desiring pregnancy. The most common intervention is endometrial injury performed using a pipelle. In the context of an IVF cycle, endometrial injury is performed some time prior to embryo transfer and can be performed as an office procedure, with or without ultrasound guidance. To perform endometrial injury, a speculum is inserted into the vagina and the external cervical os is located. A pipelle or similar device is then introduced through the external os and advanced until it reaches the uterine fundus and a sample of the endometrium is retrieved by suction and rotation within the uterine cavity. The movements made to obtain the sample are believed to result in some beneficial disturbance or "injury" to the endometrium, which may facilitate implantation and therefore increase the chance of pregnancy.

How the intervention might work

The underlying mechanism of how endometrial injury may improve endometrial receptivity remains unclear, however several pathways have been hypothesised. The first hypothesis suggests that the mechanical effect of local injury to the proliferative endometrium induces endometrial decidualisation, a process that naturally occurs in preparation for pregnancy and therefore favours implantation (Li 2009; Zhou 2008). A second hypothesis is that the injury induces a wound-healing response, which involves recruitment of immune system cells to the site of healing (Siristatidis 2014), as it is associated with a significant increase in the secretion of cytokines, interleukins, growth factors, macrophages and dendritic cells - all of which are beneficial for embryo implantation (Gnainsky 2010; Li 2009). Recruited immune cells are capable of living for months and are able to differentiate into tissue-resident macrophages or dendritic cells, thus playing a direct role in decidual development and embryo implantation (Siristatidis 2014). Uterine natural killer (NK) cells are a major source of immunoregulatory cytokines in the endometrium and are thought to be reduced in numbers during controlled ovarian stimulation (Siristatidis 2014). Endometrial injury may increase the quantity of NK cells within the endometrium, restoring these to sufficient numbers (Junovich 2011). Cytokines, growth factors and NK cells are also responsible for increased angiogenesis, thereby providing adequate blood flow to the tissue and preventing embryo rejection (Siristatidis 2014). A third hypothesis is related to the observation that ovarian stimulation during IVF leads to abnormal maturation of the endometrium, such that it is advanced at the time of embryo transfer and may be less receptive to an implanting embryo (Lass 1998; Ubaldi 1997). This hypothesis suggests that endometrial injury retards endometrial maturation, leading to better synchronicity between the endometrium and the transferred embryo (Li 2009).

Why it is important to do this review

The first published study examining this intervention suggested it could improve implantation (Barash 2003), and this sparked a series of trials investigating this IVF'add on'. Subsequently the intervention was adopted as a routine intervention in many clinics worldwide (Lensen 2016b; Spencer 2016). Several laboratory studies have indicated that endometrial injury may induce changes in the endometrium that improve reproductive outcomes in women undergoing IVF cycles. It is necessary to identify, evaluate and summarise the evidence for endometrial injury as a fertility treatment or 'add on' in women undergoing IVF cycles, to enable evidence-based medicine to be practised.

If endometrial injury is beneficial, it will help many women and couples to conceive from IVF. Similarly, if endometrial injury is of no benefit, or is detrimental to a couple's chances of a having a baby through IVF, then it can be abandoned as a technique, which currently costs patients as much as £400 in some clinics (Lensen 2016b), and is often considered to be painful.

OBJECTIVES

To assess the effectiveness and safety of endometrial injury performed before embryo transfer in women undergoing in vitro fertilisation (IVF), including intracytoplasmic sperm injection (ICSI) and frozen embryo transfer.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) were considered eligible; quasi- and pseudo-randomised trials were not included. Cross-over trials were eligible for inclusion for completeness, but only data from the first phase would be pooled in the meta-analysis because this design is not valid in the context of subfertility trials (Vail 2003). However, no cross-over trials were identified .

Types of participants

Women undergoing IVF (including ICSI and embryo transfer).

Types of interventions

The studied intervention is intentional endometrial injury performed within six months before IVF. We planned to include studies evaluating the following comparisons: (1) endometrial injury versus no intervention or a sham procedure; (2) higher versus lower degree of endometrial injury (e.g. pipelle versus hysteroscopy); and (3) different numbers of interventions (e.g. one procedure versus the procedure performed twice at two different time points).

Types of outcome measures

Primary outcomes

Effectiveness

- Live birth per woman randomised.

Ongoing pregnancy, defined as a clinical pregnancy of 12 or more weeks' gestation, was used as a surrogate for live birth in cases where studies did not report live birth but reported ongoing pregnancy.

Adverse events

- Miscarriage per woman randomised. Where possible, the definition used was the loss of a clinical pregnancy. In some cases, the number of miscarriages was calculated as the difference between the number of live births and clinical pregnancies, and in some cases the number of miscarriages was taken as reported in the paper.

Secondary outcomes

Effectiveness

- Clinical pregnancy per woman randomised, defined as the presence of one or more gestational sacs or heartbeats on ultrasound at approximately six to eight weeks gestation.

Adverse events

- Multiple gestation per woman randomised.
- Pain reported during the intervention, as measured by any validated qualitative or quantitative scale.
- Abnormal bleeding during or after the intervention.

Search methods for identification of studies

We searched for RCTs in accordance with a search strategy developed in consultation with the Information Specialist for the Cochrane Gynaecology and Fertility Group (CGF). We applied no language restriction.

Electronic searches

We performed the updated search on 15 June 2020 in the following databases:

- the CGF Specialised Register, ProCite platform, searched 15 June 2020 (Appendix 1);
- CENTRAL via the Cochrane Register of Studies (CRSO), Web platform, searched 15 June 2020 (Appendix 2);
- MEDLINE, OVID platform, searched from 1946 to 15 June 2020 (Appendix 3);
- Embase, OVID platform, searched from 1980 to 15 June 2020 (Appendix 4);
- PsycINFO, OVID platform, searched from 1806 to 15 June 2020 (Appendix 5);
- CINAHL, the Cumulative Index to Nursing and Allied Health Literature, EBSCO platform, searched from 1961 to 15 June 2020 (Appendix 6);
- LILACS, Latin American Caribbean Health Sciences Literature, Web platform, searched 15 June 2020 (Appendix 7);
- Epistemonikos, Web platform, searched 15 June 2020 (Appendix 8);
- DARE, the Database of Abstracts of Reviews of Effects, OVID platform, 2005 to November 2012 (Appendix 9).

We searched for ongoing trials on clinicaltrials.gov (http://www.clinicaltrials.gov/), and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (http://ictrptest.azurewebsites.net/Default.aspx). We searched for conference abstracts on the Web of Science and for grey literature on OpenGrey, and we handsearched for abstracts from the European Society of Human Reproduction and Embryology 2020.

Searching other resources

We searched the reference lists of included and excluded trials, other systematic reviews of this intervention and contacted experts in the field for any additional trials.

Data collection and analysis

Selection of studies

Review authors (from SFL, AG, SA) assessed eligibility independently in duplicate and in a standardised manner. Any disagreements were resolved by discussion or consultation with a third review author.

Data extraction and management

We (from SFL, AG, CON, WPM, NR-F) extracted data from eligible trials using a data extraction form that had been designed and pilot-tested by the review authors. When studies had multiple publications, we used the main trial report as the reference and obtained additional details from secondary papers. We attempted to correspond with study investigators to resolve data queries as required. Data extraction was undertaken in duplicate and disagreements were resolved by discussion.

Assessment of risk of bias in included studies

Two review authors independently assessed methodological quality and data collection by using the Cochrane risk of bias assessment tool (Higgins 2011). We assessed selection bias (random sequence generation and allocation concealment), attrition bias (incomplete outcome data), reporting bias (selective reporting), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessors) and other biases (other problems that could put a trial at high risk of bias, including lack of adequate trial registration). Studies were considered low risk for performance bias if any sham procedure was used in the control arm which was likely to blind participants to their allocation. Only studies reporting subjective outcomes such as pain during the procedure or bleeding following the procedure were judged for detection bias, as it was considered that knowledge of trial allocation would not affect the assessment of objective outcomes such as clinical pregnancy and live birth. Due to recent

publications which have suggested potential methodological issues with this cohort of studies (Li 2019), we elected to conduct a number of additional assessments on the included studies, some of which were considered to fall under the umbrella of 'Other' risk of bias. These included: lack of prospective trial registration, using Retraction Watch to search for publication retractions among trial authors, high publication rate of randomised trials by authors in the last 10 years (with particular focus on cases where authors had published many trials as first author), and careful scrutiny for any unlikely or implausible study characteristics such as high recruitment rates (per centre per month), inconsistencies in reporting of trial data (e.g. pregnancies that are not accounted for in studies that follow women to live birth). We presented and described all judgements in the conclusions portion of the Risk of bias in included studies tables.

Measures of treatment effect

We summarised the effects of the intervention as odds ratios (ORs) for binary outcomes (live birth, clinical pregnancy, miscarriage) and as mean differences (MDs) for continuous outcomes (pain). We evaluated the precision of the estimates by using the 95% confidence interval (CI). We considered the clinical relevance of all comparisons while taking into account the precision of the estimates. We planned to determine the number needed to treat for an additional beneficial outcome (NNTB) or for an additional harmful outcome (NNTH) when a significant difference was observed.

Unit of analysis issues

We used the number of woman randomised as the denominator for all outcomes. No 'per cycle' data were included.

Dealing with missing data

We analysed the data on an intention-to-treat (ITT) basis as far as possible and attempted to obtain missing data from the trial researchers. We assumed that participants who dropped out after randomisation (e.g. because of cycle cancellation), or who were lost-to-follow up or withdrew, did not achieve clinical pregnancy or live birth; no other assumptions were made.

Assessment of heterogeneity

We pooled data in a meta-analysis only when risk of bias was not substantial and the clinical and methodological characteristics of the included studies were considered to be sufficiently similar for meta-analysis to provide a clinically meaningful summary. We assessed heterogeneity using I^2 and considered $I^2 > 50\%$ to indicate substantial heterogeneity.

Assessment of reporting biases

We tried to minimise the potential impact of reporting biases by performing a comprehensive search for eligible studies including manual searching of conference proceedings and trial registration websites, and by looking for duplication of data. We performed funnel plot analysis when more than 10 studies were included in a comparison. When possible, we used published protocols and prospective trial registration pages for included studies to investigate selective reporting (i.e. comparisons of outcomes listed in the study protocol versus outcomes reported in papers).

Data synthesis

We carried out statistical analysis of the data in Review Manager (RevMan 5.4.1 and RevMan Web). When we considered studies to be sufficiently similar, we combined data using a fixed-effect model.

For this update of the review, we planned three comparisons.

1. Endometrial injury versus no injury/sham procedure.
2. Higher versus lower degree of endometrial injury (e.g. pipelle versus Tao brush).
3. Different numbers of interventions (e.g. one procedure versus multiple procedures).

However, we only identified trials for the first and second comparison.

These three comparisons are new to this updated review. In the previous version of the review, comparisons included a timing of component, depending on when the endometrial injury was performed in the IVF cycle. In this review, the effect of timing of endometrial injury was instead investigated in subgroup analysis. Further, comparison three has been added.

Subgroup analysis and investigation of heterogeneity

We conducted five different subgroup analyses to assess treatment effects within different subgroups.

We planned to conduct subgroup analyses based on the presence of recurrent implantation failure (RIF), because women who have impaired implantation ability are, theoretically, a group with better potential to benefit from the intervention. In some cases it was possible to obtain subgrouped data from the paper or from author correspondence, in which case the study was split across subgroups. The trials were broadly grouped as per published classifications (Polanski 2014) into:

- women with recurrent or previous implantation failure (≥2 previous embryo transfers);
- women having their first or second IVF cycle (≤1 previous embryo transfers);
- trials in which the inclusion criteria permitted any women regardless of previous IVF exposure, or where it was unclear.

In undertaking the previous update to this review (Nastri 2015), we observed that in several RCTs, some degree of intrauterine manipulation was also performed in the control groups. Such manipulation occurred by insertion of an instrument - such as a hysteroscope or a uterine sound - into the uterine cavity as part of the standard treatment or as a sham procedure. As such intrauterine manipulation probably causes some degree of endometrial injury, it may reduce the observed differences in reproductive outcomes caused by the intervention. To assess this, we performed a second subgroup analysis according to the type of control intervention provided:

- no intrauterine manipulation in the control group;
- intrauterine manipulation in the control group.

A third subgroup analysis concerns the timing of the endometrial injury procedure relative to the IVF cycle. This analysis was undertaken as it is suggested that the timing of the procedure may be important, as studies performing the procedure in the luteal

phase of the cycle prior to embryo transfer have reported benefit from the procedure, whereas studies performing the procedure on the day of oocyte retrieval reported harm (Karimzade 2010). In the previous iteration of this review (Nastri 2015), the timing of the endometrial injury was embedded in the main comparisons, but in this update the effect of timing of the injury was examined with the following subgroup analyses:

- follicular phase prior cycle;
- luteal phase prior cycle;
- early follicular phase IVF cycle;
- late follicular phase IVF cycle.

Studies performing endometrial injury more than once across two different time points, or permitting the procedure to be performed anytime in a broad window, were not considered for this subgroup analysis.

A fourth subgroup analysis introduced in this update to the review concerns the intensity of the intervention, as a less disruptive procedure, such as one conducted with a Tao brush, may cause a different effect to the endometrium than a procedure conducted with a more invasive instrument such as a Novak curette. The subgroups used were:

- low intensity;
- moderate intensity;
- high intensity.

Lastly, it was considered that the timing and intensity of the procedure may both be important to the effect of the procedure: for example, an intense procedure performed close to the time of embryo transfer may be harmful, whereas an intense procedure performed in the cycle prior to the embryo transfer could be beneficial, allowing sufficient healing time prior to possible implantation. For this reason, the fifth subgroup analysis was a combination of factors in the third and fourth analyses: intensity and timing of the procedure:

- follicular phase prior cycle and low intensity;
- follicular phase prior cycle and moderate intensity;
- follicular phase prior cycle and high intensity;
- luteal phase prior cycle and low intensity;
- luteal phase prior cycle and moderate intensity;
- luteal phase prior cycle and high intensity;
- early follicular phase IVF cycle and low intensity;
- early follicular phase IVF cycle and moderate intensity;
- early follicular phase IVF cycle and high intensity;
- late follicular phase IVF cycle and low intensity;
- late follicular phase IVF cycle and moderate intensity;
- late follicular phase IVF cycle and high intensity.

Sensitivity analysis

The primary analysis was restricted to studies at low risk of selection bias and other bias, for all review outcomes. We conducted sensitivity analyses to determine whether review conclusions were robust to arbitrary decisions made regarding eligibility and analysis. These analyses included consideration of whether review conclusions would have been different if eligibility had been restricted to studies without high risk of bias in any domain, and including all studies regardless of risk of bias. This was a post-hoc decision and a change from the review protocol.

Summary of findings and assessment of the certainty of the evidence

We prepared a summary of findings table to evaluate the overall certainty of the body of evidence for the main review outcomes (live birth, clinical pregnancy, miscarriage) using GRADE (Grades of Recommendation, Assessment, Development and Evaluation) criteria: study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness, publication bias, for the comparison 'Endometrial injury versus control' (no procedure or a sham procedure). We prepared a second table for the comparison 'Higher versus lower degree of injury'. We justified and documented judgements about evidence certainty (high, moderate, low and very low) and incorporated this into reporting of results for live birth, clinical pregnancy and miscarriage (GRADEpro GDT, Higgins 2019).

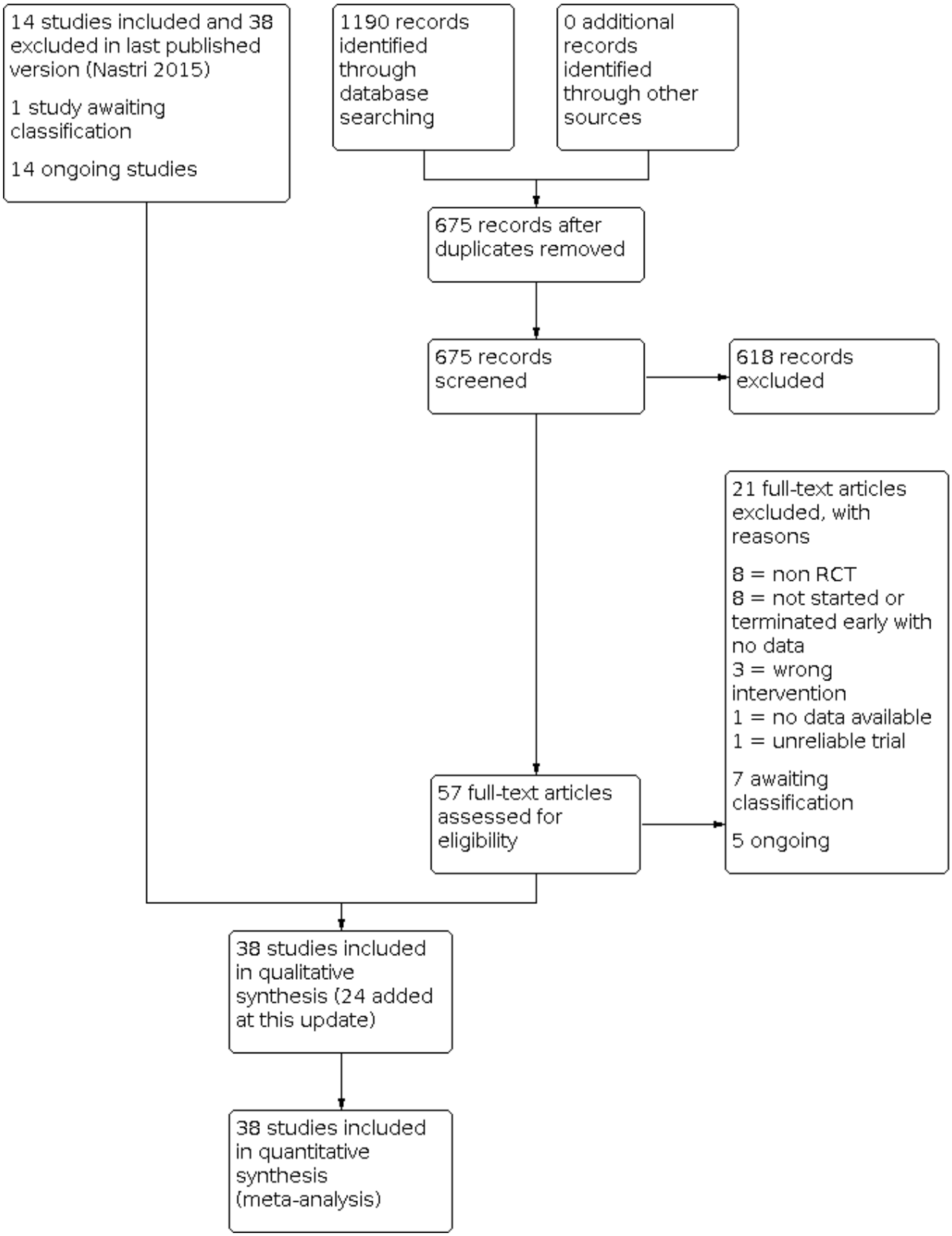
RESULTS

Description of studies

Results of the search

The first electronic search was on 14 December 2011, and new searches were carried out on 11 March 2014, 19 January 2015 and May 2017, February 2019 and June 2020. For this update, from 675 records screened on the basis of title and abstract, we identified 57 potentially eligible records; two review authors independently assessed these trials completely for eligibility and 24 new studies were included, giving 38 studies in total (Figure 1.

Figure 1. Study flow diagram.



Included studies

Study design and setting

We included 38 parallel-design RCTs in this review. All were two-arm trials except for one study which had four arms, comparing endometrial injury in the luteal versus proliferative phases with two placebo procedures at the same time (Liu 2017). The majority of studies were published as full-text articles, however six were available as conference abstracts only (Hur 2012, Karim Zadeh 2008; Merriam 2017; Metwally 2020; Polanski 2015; Zygula 2016), however extensive author correspondence was available in some cases. One study identified from the trial registration webpage was not published at all, however the authors provided the outcome data (Wolff 2018).

Most trials were single-centre trials and were conducted in Brazil (Nastri 2013), China (Liu 2017; Xu 2015), Belgium (Mackens 2020), Egypt (Maged 2018; Sherif 2018), Hong Kong (Mak 2017; Yeung 2014), India (Narvekar 2010; TK 2017;), Iran (Aflatoonian 2016 Karim Zadeh 2008; Karimzadeh 2009; Karimzade 2010; Safdarian 2011), Italy (Pecorino 2018), Israel (Baum 2012), Poland (Zygula 2016), South Korea (Hur 2012), Spain (Izquierdo Rodriguez 2020), Turkey (Gurgan 2019; Guven 2014; Inal 2012), the UK (Polanski 2015), and the USA (Eskew 2018; Merriam 2017; Wolff 2018). Eleven studies were conducted at more than one centre: in Canada (Hilton 2019), China (Tang 2020), Denmark (Berntsen 2020; Olesen 2019), Egypt (Gibreel 2015), France (Frantz 2019), Iran (Shahrokh-Tehraninejad 2016), the Netherlands (van Hoogenhuijze 2020), the UK (Metwally 2020); one in Egypt and Saudi Arabia (Shohayeb 2012), and one across 13 centres in New Zealand, Australia, Belgium, Sweden and the UK (Lensen 2019).

Author correspondence with 13 trials resulted in additional or modified outcome data not presented in the published materials (Eskew 2018; Gurgan 2019; Izquierdo Rodriguez 2020; Maged 2018; Merriam 2017; Olesen 2019; Pecorino 2018; Polanski 2015; Nastri 2013; Shohayeb 2012; Tang 2020; van Hoogenhuijze 2020; Wolff 2018).

Participants

The studies included 8915 women: 4467 women in the intervention groups and 4448 women in the control groups. Seventeen studies included only women who had undergone previous unsuccessful IVF attempts (TK 2017; Baum 2012; Berntsen 2020; Gibreel 2015; Gurgan 2019; Karim Zadeh 2008; Karimzadeh 2009; Narvekar 2010; Olesen 2019; Pecorino 2018; Shahrokh-Tehraninejad 2016; Shohayeb 2012; Tang 2020; TK 2017; van Hoogenhuijze 2020; Wolff 2018; Zygula 2016); 13 included women regardless of the number of previous attempts (Aflatoonian 2016; Eskew 2018; Guven 2014; Izquierdo Rodriguez 2020; Lensen 2019; Mackens 2020; Mak 2017; Merriam 2017; Nastri 2013; Polanski 2015; Safdarian 2011; Xu 2015; Yeung 2014); five studies included only women undergoing their first IVF cycle (Hur 2012; Maged 2018; Metwally 2020; Liu 2017; Karimzade 2010); and two recruited women undergoing either their first or second cycle (Frantz 2019; Hilton 2019). One study included women who were either undergoing their first IVF cycle, or had not had any previous unsuccessful cycles (Sherif 2018).

Interventions

All except one of the included studies (Merriam 2017), compared endometrial injury versus either no procedure or a placebo procedure, prior to or as part of an IVF cycle. Most trials used a pipelle to perform the endometrial injury, however a Novak curette was used in three studies (Karimzade 2010; Karim Zadeh 2008; Shohayeb 2012), a modified cook catheter was used in one trial (Sherif 2018), scissors in one trial (Gurgan 2019), and forceps in another (Berntsen 2020). Most studies compared endometrial injury to no procedure, however a number of studies used a placebo procedure involving placement of the catheter or cotton bud inside the cervix (Baum 2012; Liu 2017; Mak 2017; Wolff 2018), drying the cervix with gauze (Nastri 2013), placement of catheter next to cervix (Eskew 2018), and insertion of a uterine sound (Gibreel 2015). Additionally, a number of the studies conducted the endometrial injury concurrently with hysteroscopy (Berntsen 2020; Gurgan 2019; Narvekar 2010; Shohayeb 2012), or instillation of granulocyte colony-stimulating factor (Xu 2015), and the control arms in these studies also underwent these procedures in all but two trials (Berntsen 2020; Gurgan 2019). In one study, the researchers compared a pipelle curette with a Shepard insemination catheter (Merriam 2017).

Most studies performed the procedure only once, however it was performed twice in five studies: between days 9–12 and days 21–24 in the cycle before the IVF cycle (Baum 2012), twice between days 21-26 of the prior cycle (Gibreel 2015), twice within one week during the luteal phase of the prior cycle (Inal 2012), once during hysteroscopy between days 7-10 and again between days 24-25 of the prior cycle (Narvekar 2010), and twice within 48 hours during the luteal phase of the prior cycle (TK 2017).

Most studies conducted the procedure in the cycle immediately prior to the embryo transfer cycle, either in the luteal phase (Aflatoonian 2016; Eskew 2018; Frantz 2019; Gibreel 2015; Hilton 2019; Inal 2012; Izquierdo Rodriguez 2020; Karim Zadeh 2008; Karimzadeh 2009; Maged 2018; Mak 2017; Merriam 2017; Metwally 2020; Nastri 2013; Olesen 2019; Pecorino 2018; Polanski 2015; Safdarian 2011; Shahrokh-Tehraninejad 2016; TK 2017; van Hoogenhuijze 2020; Wolff 2018; Yeung 2014; Zygula 2016), or follicular phase (Berntsen 2020; Gurgan 2019; Shohayeb 2012; Tang 2020). A smaller number of studies conducted the procedure in the embryo transfer cycle, either in the early follicular phase (Guven 2014; Hur 2012; Mackens 2020; Sherif 2018), or in the late follicular phase (Karimzade 2010; Xu 2015). Four studies performed endometrial injury at multiple time points, either performing the procedure on multiple occasions or permitting the procedure to take place at any time across a broad window before embryo transfer (Baum 2012; Liu 2017; Lensen 2019; Narvekar 2010).

Outcomes

Thirty trials reported live birth; this includes four trials that reported only ongoing pregnancy, which was used as a surrogate for live birth (Aflatoonian 2016; Frantz 2019; Karimzade 2010; Maged 2018), and one trial that reported ongoing pregnancy/live birth (Mak 2017).

- 31/38 trials reported miscarriage, or the miscarriage rate was calculated from the available rates of live birth minus clinical pregnancy
- 38/38 trials reported clinical pregnancy
- 20/38 trials reported multiple pregnancy
- 10/38 trials reported pain
- 9/38 trials reported bleeding.

Excluded studies

A total of 24 studies were excluded for the following reasons: the study was not randomised (11 studies); the trial was never initiated or was terminated early with no available data (eight studies); the intervention was not eligible (three studies); no data were available (one study); and there was information available from authors that suggested the data from one trial were unreliable (one1 study) (Figure 1, Characteristics of excluded studies).

Ongoing studies

A further 19 studies appear to be ongoing according to either the trial registration page and/or from author correspondence (Characteristics of ongoing studies).

Studies awaiting classification

A total of eight studies are pending classification (Studies awaiting classification).

Risk of bias in included studies

In general the studies included in this review were small (median sample size 157, interquartile range (IQR)100 to 280) and therefore had limited power to detect clinically-relevant differences in the outcomes included in this review. Many of the trials were also associated with serious risks of bias; every trial had one or more unclear or high risk of bias (Figure 2, Characteristics of included studies).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

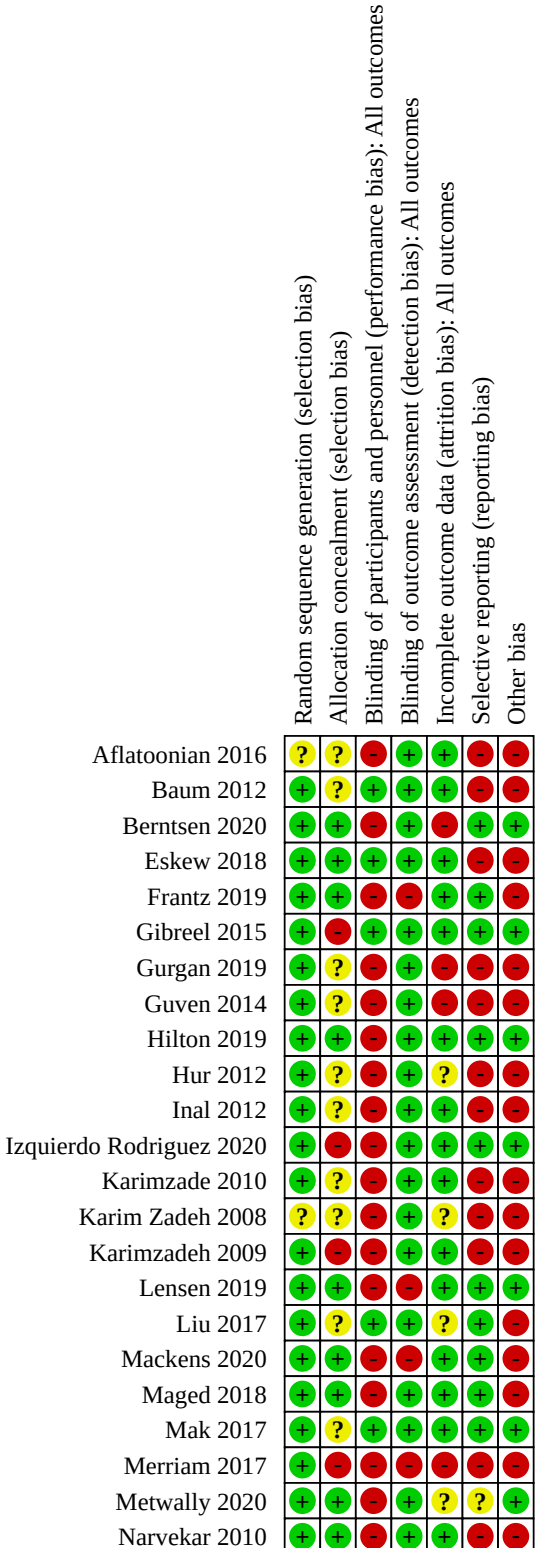
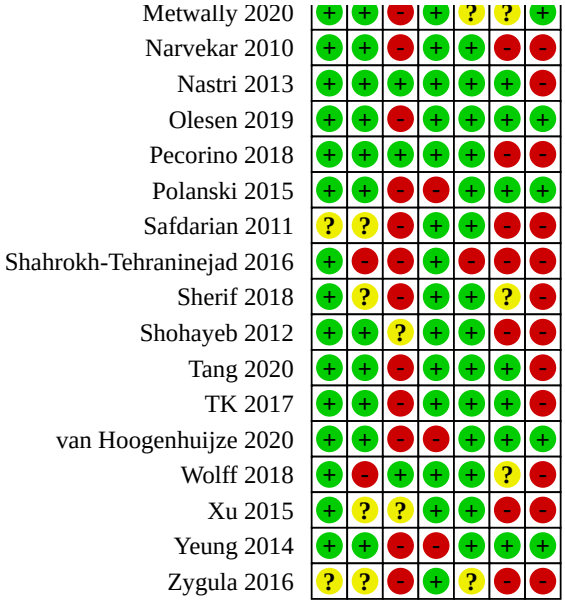


Figure 2. (Continued)



Allocation

Random sequence generation

The majority of studies used adequate methods for random sequence generation and were deemed to be at low risk for this domain. Three studies claimed to be randomised but did not report the method used for randomisation (Karim Zadeh 2008; Zygula 2016) or reported apparently conflicting information regarding the process of recruitment and allocation (Aflatoonian 2016); and were therefore judged to be at unclear risk of bias. Another trial reported that quote: "participants were randomly selected on the basis of their agreement to undergo endometrial biopsy" and it is not clear if the study was truly randomised (Safdarian 2011). One study is described as being non-randomised on the trial registration page and is described in the paper as being a quote: "prospective case-control study" however the authors confirmed in correspondence that computer-based randomisation was used, therefore this study was graded as low risk (Guven 2014).

Allocation concealment

Eighteen studies used adequate methods for concealment of the random sequence and were deemed to be at low risk of selection bias.

Eleven studies did not report an attempt to conceal the allocation (Aflatoonian 2016; Baum 2012; Gurgan 2019; Hur 2012; Karim Zadeh 2008; Karimzade 2010; Liu 2017; Safdarian 2011; Sherif 2018; Xu 2015; Zygula 2016); and were judged to be at unclear risk of bias. A further three trials reported to use envelopes but it is unclear whether these met the SNOSE (sequentially numbered opaque sealed envelopes) criteria (Guven 2014; Inal 2012; Mak 2017).

Six studies were graded as high risk: two trial teams confirmed the envelopes used were not SNOSE (sequentially numbered, opaque sealed envelopes), and therefore these trials were graded as high risk (Gibreel 2015; Merriam 2017); two studies reported that patients drew numbers out of a bag to determine their allocation, and no safeguards were described to prevent the patients from replacing the paper and drawing another, therefore these studies were graded as high risk (Karimzadeh 2009; Shahrokh-Tehraninejad 2016); a further two studies reported during author correspondence to have used an open list of allocations (Izquierdo Rodriguez 2020; Wolff 2018).

Blinding

Performance bias

Most studies were rated as high risk for performance bias as no blinding of participants or personnel was employed. In a number of cases, imbalances in the number of women reaching embryo transfer or undergoing single versus double-embryo transfer were observed, which while minor imbalances, may have resulted from knowledge of trial allocation (Lensen 2019; Metwally 2020; van Hoogenhuijze 2020).

Studies which implemented a sham procedure were rated as low risk of bias, although it remains uncertain whether some of the sham procedures used would truly blind participants to their allocation. A number of sham procedures involved instrumentation of the cervix and uterine cavity (Gibreel 2015; Liu 2017; Pecorino 2018) or involved endocervical manipulation (Baum 2012; Mak 2017; Wolff 2018), and others involved placement of an instrument next to the cervix only (Eskew 2018; Nastri 2013). One study compared instillation of granulocyte colony stimulating factor alone with instillation in addition to endometrial injury (Xu 2015), and another study performed the procedure in addition to a hysteroscopy procedure which all women underwent (Shohayeb 2012); in these two cases it was not clear whether the participants were actually blind to their allocation or whether they were informed of it, therefore these trials were rated as unclear.

Detection bias

For the purposes of this review, lack of blinding was not considered to be a source of detection bias in studies reporting only objective outcomes such as clinical pregnancy. These trials were rated as low risk for detection bias even when no blinding was employed. For the studies reporting on pain and/or bleeding during or following the procedure, outcomes which were self-reported by participants, lack of blinding was considered a risk of detection bias. These outcomes were reported in 10 trials; three implemented a sham procedure therefore the participants were considered blind to their allocation (Liu 2017; Nastri 2013; Pecorino 2018), and the remainder were rated as high risk (Frantz 2019; Lensen 2019; Mackens 2020; Merriam 2017; Polanski 2015; van Hoogenhuijze 2020; Yeung 2014).

Incomplete outcome data

Most of the studies were rated as low risk as it appeared that there was no or only minimal attrition. For studies reported only as abstracts, unless additional information regarding attrition could be supplied by the authors, these were rated as unclear risk (Hur 2012; Karim Zadeh 2008; Metwally 2020; Zygula 2016). A further study was rated as unclear risk as it reported that all 142 women reached embryo transfer which seems unlikely, and raises the possibility that women not reaching embryo transfer were excluded (Liu 2017). One trial was rated as high risk as one of the inclusion criteria appears to only be able to be applied after randomisation (endometrium of >7 mm on day commencing progesterone supplementation) and therefore it seems likely that participants were excluded on this basis after randomisation (Shahrokh-Tehraninejad 2016). Similarly, in another trial the eligibility criteria would have been applied post-randomisation (grade I or II embryos to transfer and no failure to proceed to follicle retrieval) (Guven 2014). It is unclear how many women were excluded for these reasons. Another two trials were rated as high risk due to post-randomisation exclusions in the intervention group for women who did not undergo the injury procedure (Merriam 2017) or those with abnormalities identified (Berntsen 2020; Gurgan 2019). Further, we observed an unexplained imbalance in the number of women with cancelled or failed cycles between the two groups in one study (Gurgan 2019), and in another study, all participants from one recruiting centre were excluded due to the centre closing down and follow-up data being unavailable (Berntsen 2020).

Selective reporting

The majority of studies did not have adequate trial registration (26 studies); 11 were registered retrospectively, four were registered late (within six months of starting recruitment), nine were not registered at all, and in two cases it was unclear as the recruitment period was unknown. Studies that were not registered or registered retrospectively were rated as high risk for selective reporting, unless they reported important review outcomes including live birth and adverse events such as pain and/or bleeding, which occurred in two instances (Liu 2017; TK 2017). A total of 12 studies were registered prospectively, and these were graded as low risk if they reported all planned (review) outcomes; in one case the study was only available as an abstract which did not report all registered outcomes, and this study was rated as unclear as it is not known whether all registered outcomes will be reported by the trial team (Metwally 2020). For two trials it was unclear whether the trial registration was prospective or not, therefore these studies were rated as unclear risk (Sherif 2018; Wolff 2018).

Other potential sources of bias

Most of the studies were rated as high risk for this domain. A total of 10 trials stopped early due to: observing a significant effect (Eskew 2018; Frantz 2019; Mackens 2020; Nastri 2013; Karimzade 2010), difficulty recruiting (Berntsen 2020; Hilton 2019; TK 2017; Wolff 2018), or unclear reasons (Baum 2012). Studies stopping early for observing a positive effect were rated as high risk; even when stopping is on the basis of adequate stopping rules, the resulting data available for meta-analysis have been demonstrated to produce a biased effect (Bassler 2010). In cases where only abstract or limited information was available, we graded the study as high risk for other bias due to the potential for missing information to impact on trial eligibility or outcome data (Hur 2012; Karim Zadeh 2008; Merriam 2017; Wolff 2018; Zygula 2016). In one study it was observed that one trial arm had a significantly higher fertilisation rate, which would have favoured the intervention arm, and this study was therefore rated as high risk (Sherif 2018). Additionally, all trials which were not registered prospectively or within six months of initiating recruitment, were rated as high risk of other bias, due to the potential for undisclosed protocol changes or deviations which can cause bias.

A number of studies were also identified as having additional concerns, some of which were seen as representing a high risk of 'Other bias'. These included: inconsistency between reported outcomes (e.g. implantation and clinical pregnancy rates, leading to uncertainty in the accuracy of the data) or inconsistency in reported timelines (e.g. time between completing recruitment and submitting paper did not allow for follow-up to live birth) (Aflatoonian 2016; Inal 2012; Maged 2018; Pecorino 2018; Shohayeb 2012); a number of authors on studies had also been authors on retracted publications (Aflatoonian 2016; Gurgan 2019; Karimzade 2010; Karim Zadeh 2008; Karimzadeh 2009; Xu 2015); some studies had very high recruitment rates which may or may not be explained by the nature of the trial population or setting (Guven 2014; Karimzade 2010; Maged 2018; Safdarian 2011; Tang 2020), and some authors had a large number of published trials in recent years, which may represent an improbable workload (Aflatoonian 2016; Maged 2018; Shohayeb 2012). In most cases, the implications of these additional concerns is not clear, however we present them in this review for transparency.

In previous versions of the review, exposure of the control participants to intentional or inadvertent endometrial disruption was rated as high risk of bias, due to the potential for this exposure to dilute the observed effect of endometrial injury. However, it is now considered that this does not represent a risk of bias per se, and the effect of any manipulation in the control group is explored in the subgroup analysis.

Effects of interventions

See: **Summary of findings 1** Endometrial injury compared to control in women undergoing assisted reproductive techniques; **Summary of findings 2** Higher compared to lower degree of injury in women undergoing assisted reproductive techniques

1. Endometrial injury versus control

A total of 37 studies (8786 women) were included in this comparison. Due to the high risk of bias associated with many of the included studies, a post-hoc decision was made to restrict the primary analysis to studies at low risk of selection and other bias. A

total of eight studies are therefore included in the primary analyses for all outcomes.

Two sensitivity analyses were also conducted.

1. Excluding studies at high risk of bias in any domain, which left one remaining study included (Mak 2017). This trial evaluated endometrial injury by pipelle biopsy in the luteal phase of the cycle prior to a frozen-embryo transfer cycle.
2. Including all studies, regardless of risk of bias. However:

- Substantial statistical heterogeneity was observed when pooling all trials for the outcomes of live birth and clinical pregnancy, as the treatment effects of included trials ranged from implausibly high benefit to significant harm. To illustrate: one trial of 156 women conducted endometrial injury with a Novak curette on the day of oocyte retrieval and reported a reduced probability of conception compared to the control arm (odds ratio (OR) 0.27, 95% confidence interval (CI) 0.12 to 0.62, n =156) (Karimzade 2010). Another trial performed endometrial injury in the luteal phase of the preceding cycle and reported a high odds of live birth in women undergoing endometrial injury (OR 2.43, 95% CI 1.22 - 4.85, n = 158) (Nastri 2013). Due to the small size of most of the included trials, a large number of trials had wide confidence intervals which were consistent with benefit, no effect, or harm: three trials reported statistically significant benefit from endometrial injury and one trial reported significant harm.
- The overall risk of bias in this collection of studies was substantial, so that even if the studies were considered to be broadly comparable, the pooled estimate could have been highly misleading.

Therefore, we elected not to pool the studies for this sensitivity analysis for the outcomes of clinical pregnancy and live birth.

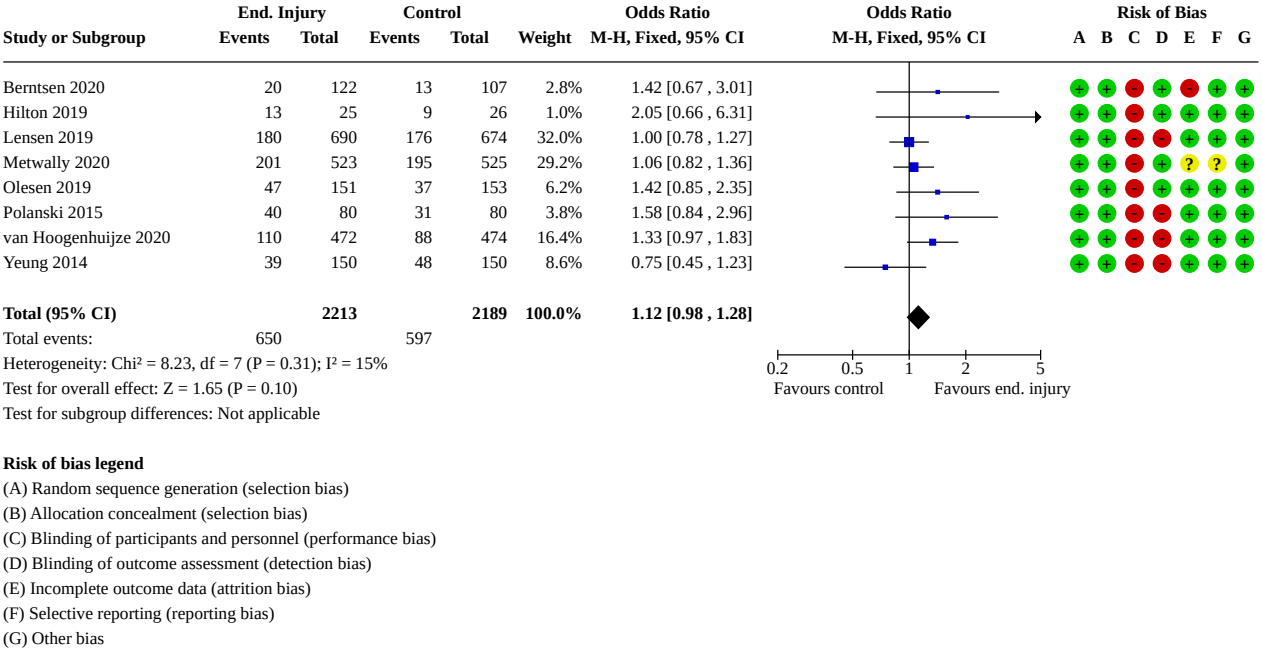
Subgroup analysis was undertaken as described in the methods for the outcomes of live birth and clinical pregnancy, and applied only to the studies included in the primary analyses. As with all subgroup analyses, the results should be interpreted with caution.

Primary outcome

1.1 Live birth per woman randomised

Live birth or ongoing pregnancy was reported in a total of 29 studies, of which eight were included in the primary analysis (Analysis 1.1, Figure 3). The effect of endometrial injury on live birth is unclear as the result is consistent with no effect, a small reduction, and an improvement (OR 1.12, 95% CI 0.98 to 1.28; participants = 4402; studies = 8; I^2 = 15%, moderate-certainty evidence). The result suggests that if the chance of live birth with IVF is usually 27%, then the chance when using endometrial injury would be somewhere between < 27% and 32%.

Figure 3. Forest plot of comparison: 1 Endometrial injury vs control, outcome: 1.1 Live birth per woman randomised (studies at low risk of selection bias and other bias).



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analyses 1.2 and 1.3 Live birth per woman randomised - Sensitivity analysis

Only one study was not associated with any high risk of bias. As this was a small trial, the result and corresponding confidence interval are wide and consistent with a wide range of possible treatment effects (OR 1.13, 95% CI 0.63 to 2.03; participants = 229; studies = 1; low-certainty evidence) (Analysis 1.2). This suggests that if the chance of live birth from IVF(or frozen embryo transfer) is normally 25%, then the chance of live birth from endometrial injury before IVF is between 18% and 41%.

Sensitivity analysis including all studies regardless of risk of bias is presented, however meta-analysis was not undertaken for the reasons stated above (Analysis 1.3).

Live birth - subgroup analysis

1.4 Subgroup analysis: presence of intrauterine manipulation in the control group

All eight included studies belonged to the same subgroup (no manipulation in the control group), as none of these studies performed any intervention in the control group (Analysis 1.4). The result of this subgroup analysis is therefore identical to the primary analysis.

1.5 Subgroup analysis: presence of recurrent implantation failure

It was not possible to pool the studies in these subgroups due to observed heterogeneity (Analysis 1.5).

1.6 Subgroup analysis: timing of endometrial injury

Studies were subgrouped based on the timing of the endometrial injury, and only two time points were applicable: the luteal phase or follicular phase of the cycle prior to the IVF cycle (Analysis 1.6). Studies that performed the injury more than once at different time points or permitted it to be performed anytime in a large window were excluded from this analysis. Among studies performing endometrial injury in the luteal phase of the cycle prior to IVF, endometrial injury may increase live birth rates (OR 1.16, 95% CI 0.99 to 1.37; participants = 2809; studies = 6; I^2 = 26%). Only one study performed endometrial injury in the follicular phase of the cycle prior to the IVF cycle, and the confidence interval associated with this study is consistent with endometrial injury being beneficial, detrimental or having no effect (OR 1.42, 95% CI 0.67 to 3.01; participants = 229; studies = 1).

1.7 Subgroup analysis: intensity of endometrial injury

Studies were subgrouped based on intensity or degree of disruption likely caused by the endometrial injury procedure (Analysis 1.7). Among studies performing a moderate-intensity injury, endometrial injury may increase live birth rates however, the confidence interval is also consistent with no effect and a small reduction (OR 1.11, 95% CI 0.97 to 1.27; participants = 4173; studies = 7; I^2 = 23%). One study performed a high-intensity endometrial injury, and the confidence interval associated with this study is consistent with endometrial injury being beneficial, detrimental or having no effect (OR 1.42, 95% CI 0.67 to 3.01; participants = 229; studies = 1).

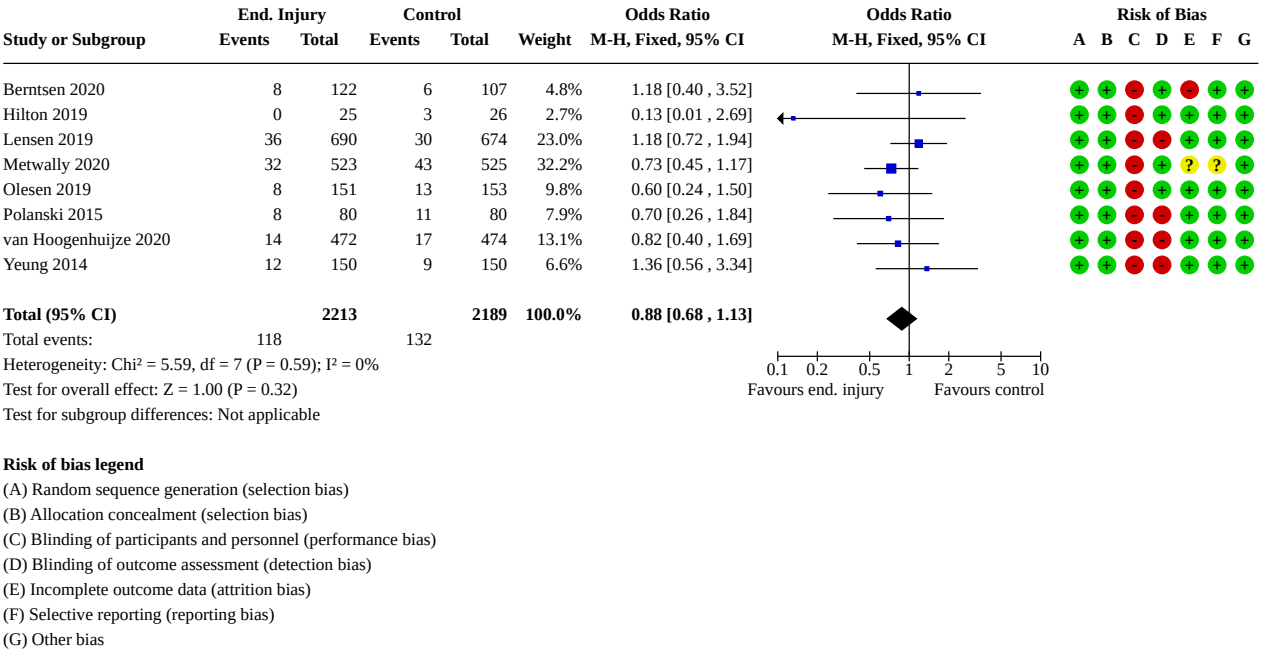
1.8 Subgroup analysis: timing and intensity of endometrial injury

Studies were subgrouped into categories based on a combination of timing and intensity of the endometrial injury procedure (Analysis 1.8). As a result, only two categories were applicable and the analysis was identical to subgrouping based on timing of endometrial injury. Among studies performing endometrial injury in the luteal phase of the cycle prior to IVF at moderate intensity, endometrial injury may increase the chance of live birth (OR 1.16, 95% CI 0.99 to 1.37; participants = 2809; studies = 6; I^2 = 26%). One study performed endometrial injury in the follicular phase of the cycle prior to the IVF cycle at high intensity, and included only 229 women. Therefore the confidence interval associated with this study is wide and consistent with endometrial injury being beneficial, detrimental or having no effect (OR 1.42, 95% CI 0.67 to 3.01; participants = 229; studies = 1).

1.9 Miscarriage per woman randomised

Miscarriage data were available for a total of 30 studies, including all eight studies included in the primary analysis. The evidence suggests that endometrial injury results in little to no difference to the chance of miscarriage (OR 0.88, 95% CI 0.68 to 1.13; participants = 4402; studies = 8; I^2 = 0%, moderate-certainty evidence) (Analysis 1.9, Figure 4). If the chance of miscarriage from IVF is normally 6.0%, then the chance of miscarriage from endometrial injury before IVF is between 4.2% and 6.8%.

Figure 4. Forest plot of comparison: 1 Endometrial injury vs control, outcome: 1.9 Miscarriage per woman randomised (studies at low risk of selection bias and other bias).



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analyses 1.10 and 1.11 Miscarriage per woman randomised - Sensitivity analysis

Only one study was not associated with any high risk of bias. As this was a small trial, the result and the corresponding confidence intervals are wide and consistent with a wide range of possible treatment effects (OR 1.17, 95% CI 0.38 to 3.58; participants = 229, low-certainty evidence) (Analysis 1.10). This suggests that if the chance of miscarriage from IVF (or frozen embryo transfer) is normally 5.3%, then the chance of miscarriage from endometrial injury before IVF is between 2.1% and 17%.

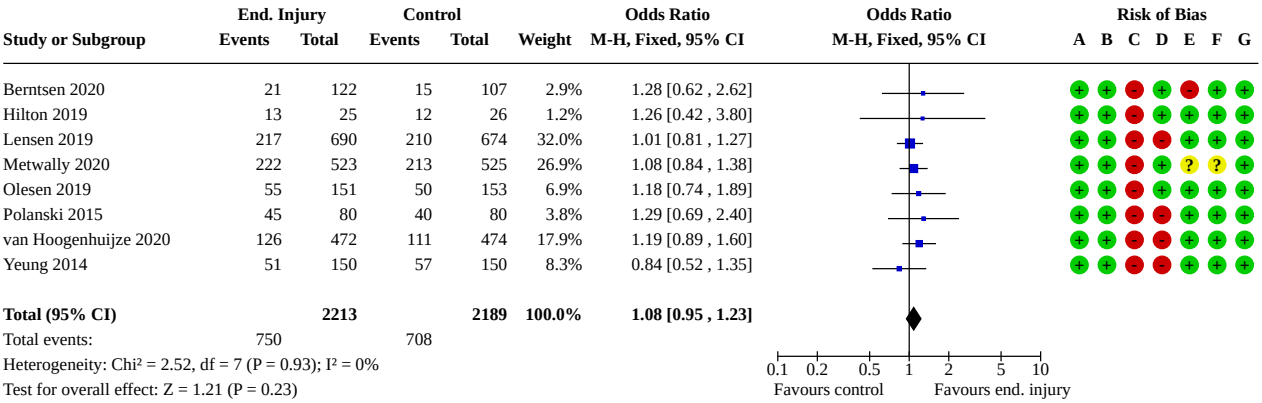
Sensitivity analysis including all studies regardless of risk of bias was also undertaken. (Analysis 1.11). The evidence suggests that endometrial injury results little to no difference to the rate of miscarriage (OR 1.03, 95% CI 0.85 to 1.25; participants = 8092; studies = 30; I^2 = 0%, low-certainty evidence). If the chance of miscarriage from IVF is normally 5.4%, then the chance of miscarriage from endometrial injury before IVF is between 4.6% and 6.7%.

Secondary outcomes

1.12 Clinical pregnancy per woman randomised

All 37 studies in this comparison reported the outcome of clinical pregnancy. The effect of endometrial injury on clinical pregnancy is unclear as the result is consistent with no effect, a small reduction, and an improvement (OR 1.08, 95% CI 0.95 to 1.23; participants = 4402; studies = 8; I^2 = 0%, moderate-certainty evidence) (Analysis 1.12, Figure 5). The result suggests that if the chance of clinical pregnancy with IVF is usually 32%, then the chance when using endometrial injury would be somewhere between 31% and 37%.

Figure 5. Forest plot of comparison: 1 Endometrial injury vs control, outcome: 1.12 Clinical pregnancy per woman randomised (studies at low risk of selection bias and other bias).



Risk of bias legend
(A) Random sequence generation (selection bias)
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(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analyses 1.13 and 1.14 Clinical pregnancy per woman randomised - Sensitivity analysis

Only one study was not associated with any high risk of bias. As this was a small trial, the corresponding confidence interval is wide and consistent with endometrial injury being associated with an increase, decrease, or no effect on clinical pregnancy rate (OR 1.16, 95% CI 0.67 to 2.02; participants = 229, low-certainty evidence) (Analysis 1.13). This suggests that if the chance of clinical pregnancy from IVF (or frozen embryo transfer) is normally 31%, then the chance of clinical pregnancy from endometrial injury before IVF is between 23% and 47%.

Sensitivity analysis including all studies regardless of risk of bias is presented, however meta-analysis was not undertaken (Analysis 1.14).

1.15 Subgroup analysis: presence of intrauterine manipulation in the control group

All eight included studies belonged to the same subgroup (no manipulation in the control group), as none of these studies performed any intervention in the control group (Analysis 1.15). The result of this subgroup analysis is therefore identical to the primary analysis.

1.16 Subgroup analysis: presence of recurrent implantation failure0

It was not possible to pool the studies in these subgroups due to observed heterogeneity (Analysis 1.16).

1.17 Subgroup analysis: timing of endometrial injury

Studies were subgrouped based on the timing of the endometrial injury, and only two time points were applicable: the luteal phase or follicular phase of the cycle prior to the IVF cycle (Analysis 1.17). Studies that performed the injury more than once at different time points or permitted it to be performed anytime in a large window were excluded from this analysis. Among studies performing endometrial injury in the luteal phase of the cycle prior to IVF, endometrial injury may increase clinical pregnancy rates (OR 1.10, 95% CI 0.94 to 1.29; participants = 2809; studies = 6; I^2 = 0%). Only one study performed endometrial injury in the follicular phase of the cycle prior to the IVF cycle, and the confidence interval associated with this study is consistent with endometrial injury being beneficial, detrimental or having no effect (OR 1.28, 95% CI 0.62 to 2.62; participants = 229; studies = 1).

1.18 Subgroup analysis: intensity of endometrial injury

Among studies performing a moderate-intensity injury, endometrial injury may increase the chance of clinical pregnancy however, the confidence interval is also consistent with no effect and a small reduction in the chance of clinical pregnancy (OR 1.07, 95% CI 0.94 to 1.22); participants = 4173; studies = 7; I^2 = 23%) (Analysis 1.18). One study performed a high intensity endometrial injury, and the confidence interval associated with this study is consistent with endometrial injury being beneficial, detrimental or having no effect (OR 1.28, 95% CI 0.62 to 2.62; participants = 229; studies = 1).

1.19 Subgroup analysis: timing and intensity of endometrial injury

Among studies performing endometrial injury in the luteal phase of the cycle prior to IVF at moderate intensity, endometrial injury may increase the chance of clinical pregnancy (OR 1.10, 95% CI 0.94 to 1.29; participants = 2809; studies = 6; I^2 = 0%) (Analysis 1.19). One study performed endometrial injury in the follicular phase of the cycle prior to the IVF cycle at high intensity, and included only 229 women. Therefore the confidence interval associated with this study is wide and consistent with endometrial injury being

beneficial, detrimental or having no effect (OR 1.28, 95% CI 0.62 to 2.62; participants = 229; studies = 1).

1.20 Multiple pregnancy per woman randomised

Multiple pregnancy data were available for a total of 21 studies, including five studies in the primary analysis. Endometrial injury may be associated with an increase, decrease, or no effect on multiple pregnancy rate (OR 1.25, 95% CI 0.80 to 1.96; participants = 3074; studies = 5; I^2 = 0%) (Analysis 1.20). The result suggests that if the chance of multiple pregnancy with IVF is usually 2.4%, then the chance when using endometrial injury would be somewhere between 1.9% and 4.5%.

Analyses 1.21 and 1.22 Multiple pregnancy per woman randomised - Sensitivity analysis

Only one study was not associated with any high risk of bias. As this was a small trial, the corresponding confidence interval is wide and consistent with endometrial injury being associated with an increase, decrease, or no effect on multiple pregnancy rate (OR 0.99, 95% CI 0.24 to 4.06); participants = 229; studies = 1) (Analysis 1.21). This suggests that if the chance of multiple pregnancy from IVF (or frozen embryo transfer) is normally 3.5%, then the chance with endometrial injury before IVF is between 0.9% and 13%.

Sensitivity analysis including all studies regardless of risk of bias was also undertaken (Analysis 1.22). The evidence suggests that endometrial injury results little to no difference to the rate of multiple pregnancy (OR 1.33, 95% CI 1.05 to 1.68; participants = 5978; studies = 20; I^2 = 0%). If the chance of multiple pregnancy from IVF is normally 4.6%, then the chance of multiple pregnancy from endometrial injury before IVF is between 4.8% and 7.4%.

1.23 Pain

Nine studies reported on pain resulting from endometrial injury, including four studies in the primary analysis. In all studies reporting this outcome, the intervention group underwent endometrial injury with a pipelle biopsy. However, as this outcome was most often collected only in the intervention arm meta-analysis was not possible for the primary analysis.

One study reported that women undergoing endometrial injury had a median pain score of 3.5/10 (IQR 1.9 to 6.0) and that 37/690 women had a score of 0/10 and six women had a score of 10/10 (Lensen 2019). Another trial asked participants if they could tolerate the pain or not (binary); 15/80 women experienced pain during the procedure, 14 were able to tolerate it and one women requested the procedure be stopped (Polanski 2015). In one study, comparing pipelle biopsy in the mid-luteal phase of the cycle prior to the IVF cycle, participants were asked to report the maximum pain they experienced directly after the procedure on a 10 cm visual analogue scale (VAS (van Hoogenhuijze 2020). In this study the median pain during the procedure was 4.5/10 (IQR 3.0 to 6.0). One further study reported only that there were no cases of serious or significant pain from endometrial injury (Yeung 2014).

1.23 Pain per woman randomised - Sensitivity analysis

In the only study with no high risk of bias, pain was not reported.

Sensitivity analysis including all studies regardless of risk of bias included nine studies. Only two of these captured pain in both arms of the study and the data are presented, however meta-analysis was not undertaken (Analysis 1.23). In addition to the pain outcomes reported in the four studies above, pain was reported by a further five studies. In one trial in which the sham procedure involved drying of the cervix with gauze, endometrial injury was associated with increased pain assessed by VAS (MD 4.60, 95% CI 3.98 to 5.22; 158 women; Analysis 1.23) (Nastri 2013). In another study using a sham procedure which involved placement of an embryo catheter into the womb, 30 (of 40 women undergoing the endometrial injury) reported pain between 5 to 7/10, six women reported pain of 2/10 and four women reported a pain score of 8/10. The authors confirmed the intervention group experienced higher pain scores (MD 1.60, 05% CI 1.14, 2.06; 80 women; Analysis 1.23) (Pecorino 2018). One study reported that 40/50 (80%) of women experienced pain, with those experiencing pain reporting a mean of 4.6/10 (standard deviation (SD) 2.1) (Frantz 2019). In 31 of these women, the pain subsided quickly, however in the six patients for whom pain did not resolve quickly, three felt a contraction-like pain, one patient felt period-like pain, one patient felt piercing pain, and one patient a stabbing pain. In one study, evaluating pipelle biopsy between days six to eight of ovarian stimulation, women were asked if they experienced excessive pain (yes/no) and 3/100 women reported they experienced excessive pain (Mackens 2020). One further study reported only that there were no cases of serious or significant pain from endometrial injury (Liu 2017).

1.24 Bleeding

Nine studies reported on bleeding resulting from endometrial injury, including four studies in the primary analysis. However as the outcome was most often collected only in the intervention arm, it was not possible to pool any of these results.

One study reported that 263/690 (38%) women experienced spotting the day following the procedure; 24/690 (4%) women experienced significant bleeding; and two women reported excessive bleeding (Lensen 2019). Another study reported that 54% of women undergoing pipelle biopsy experienced some blood loss in the following week. however that this was mostly minimal only, with 7% of participants reporting moderate or severe bleeding (van Hoogenhuijze 2020). The remaining two trials reported that no excessive/significant/heavy bleeding was noted (Polanski 2015; Yeung 2014).

1.24 Bleeding per woman randomised - Sensitivity analysis

In the only study with no high risk of bias, bleeding was not reported.

In addition to the bleeding outcomes reported in the four studies above, bleeding was reported by a further five studies. One study reported that 22/47 (47%) women experienced bleeding after the procedure (Frantz 2019). Another trial reported that a small amount of bleeding (< 50 mL) was registered during injury in 31/40 (77%) participants; which implied no bleeding in the control arm, in whom the sham procedure involved placing an embryo catheter into the womb (Pecorino 2018). One trial reported that bleeding during the procedure occurred in most participants in the intervention group, but that no participants complained of bleeding in the following days (Nastri 2013). In another study, only 5% of participants reported bleeding between the endometrial injury (which was performed between days six to eight of ovarian stimulation) and oocyte retrieval (Mackens 2020). One further trial reported that no excessive/significant/heavy bleeding was noted (Liu 2017).

Other analyses

We constructed funnel plots for the outcomes of live birth and clinical pregnancy, and did not identify any evidence of publication bias.

2. Higher compared to lower degree of injury

Only one study was included in this comparison, which compared endometrial injury using two different instruments, a pipelle catheter and a Shepard catheter, between day 21 to 27 of the cycle prior to the IVF cycle. In this case, the researchers anticipated that the Shepard catheter would cause a lesser degree of endometrial injury. Due to high risk of bias, this study was not included in the primary analysis, and all analyses below represent sensitivity analyses including all studies.

2.1 Live birth - Sensitivity analysis

As the evidence was graded as very low certainty, we are uncertain whether choice of catheter between pipelle and Shepard for endometrial injury has any impact on the chance of live birth following IVF (OR 1.28, 95% CI 0.31 to 5.37; participants = 129, very low-certainty evidence) (Analysis 2.1). This suggests that if the chance of live birth using a Shepard catheter for endometrial injury prior to IVF is normally 5.6%, then the chance with a pipelle catheter is between 1.8% and 24%.

2.2 Miscarriage - Sensitivity analysis

As the evidence was graded as very low certainty, we are uncertain whether choice of catheter between pipelle and Shepard for endometrial injury has any impact on the chance of miscarriage following IVF (OR 1.28, 95% CI 0.31 to 5.37; participants = 129, very low-certainty evidence) (Analysis 2.2). This suggests that if the chance of miscarriage using a Shepard catheter for endometrial injury prior to IVF is normally 5.6%, then the chance with a pipelle catheter is between 1.8% and 24%.

2.3 Clinical pregnancy - Sensitivity analysis

As the evidence was graded as very low certainty, we are uncertain whether choice of catheter between pipelle and Shepard for endometrial injury has any impact on the chance of clinical pregnancy following IVF (OR 1.31, 95% CI 0.46 to 3.73; participants = 129, very low certainty-evidence) (Analysis 2.3).This suggests that if the chance of clinical pregnancy using a Shepard catheter for endometrial injury prior to IVF is normally 11%, then the chance with a pipelle catheter is between 5.4% and 32%

2.4 Pain - Sensitivity analysis

As the evidence was graded as very low certainty, we are uncertain whether choice of catheter between pipelle and Shepard for endometrial injury has any impact on the degree of pain experienced during endometrial injury (mean difference (MD) 1.10, 95% CI 0.29 to 1.91; participants = 129) (Analysis 2.4).

DISCUSSION

Summary of main results

Endometrial injury versus no injury

The aim of this review was to assess the evidence regarding the effectiveness and safety of endometrial injury in women undergoing IVF. A total of 38 published and unpublished trials involving 8915 women were included in this review, of which 37 were included in this comparison. Many of the included trials were of poor quality, being mostly small and associated with various risks of serious bias. Owing to the observed high risk of bias and substantial heterogeneity between studies, we made a post-hoc decision to restrict the primary analysis to studies at low risk of selection and other bias; this left only eight studies included in the primary analyses.

Based on the results of the primary analyses, the effect of endometrial injury is unclear as the results are consistent with no effect, a small reduction, and an improvement in the chanceof live birth (odds ratio (OR) 1.12, 95% confidence interval (CI) 0.98 to 1.28; participants = 4402, studies = 8, moderate-certainty evidence) and clinical pregnancy (OR 1.08, 95% CI 0.95 to 1.23; participants = 4402; studies = 8; I^2 = 0%, moderate-certainty evidence). For example, the results suggest that if the chanceof clinical pregnancy with IVF is usually 32%, then the chancewhen using endometrial injury would be somewhere between 31% and 37%. We are therefore uncertain whether endometrial injury improves the chanceof live birth or clinical pregnancy in women undergoing IVF. Endometrial injury appears to make little or no difference to the chance of miscarriage (OR 0.88, 95% CI 0.68 to 1.13; participants = 4402; studies = 8; I^2 = 0%, moderate-certainty evidence), or multiple pregnancy (OR 1.25, 95% CI 0.80 to 1.96; participants = 3074; studies = 5; I^2 = 0%). For example, if the chance of miscarriage from IVF is normally 6.0%, then the chance of miscarriage from endometrial injury before IVF is somewhere between 4.2% and 6.8%.

A small number of included trials reported the adverse events of pain and bleeding during and following the procedure. Endometrial injury was associated with mild-moderate pain, reported between 3.5 to 4.5 out of 10. The procedure was also associated with some bleeding, but only rarely was this considered significant or excessive. These outcomes were reported in different ways in each trial, and because of this and the observed statistical heterogeneity, pooling was not possible. However, it is possible to conclude that endometrial injury is a somewhat painful procedure which may cause some bleeding, however it is unlikely to be serious or significant.

Sensitivity analysis excluding studies rated as high-risk of bias in any domain left only one trial, which was small with wide confidence intervals around the results for most outcomes. Therefore the study results are consistent with benefit, harm or no effect for the outcomes of live birth (OR 1.13, 95% CI 0.63 to 2.03; participants = 229, low-certainty evidence) and clinical pregnancy (OR 1.16, 95% CI 0.67 to 2.02; participants = 229, low-certainty evidence). This suggests that if the chance of live birth from IVF (or frozen embryo transfer) is normally 25%, then the chance of live birth from endometrial injury before IVF is between 18% and 41%. As this analysis was restricted to only one trial, the generalisability of this result is unclear - particularly as this trial was conducted in women undergoing a frozen embryo transfer cycle. Additionally, this study was rated as unclear risk of bias for the domain of allocation concealment.

Sensitivity analysis including all trials, regardless of risk of bias, was also undertaken. Due to risk of bias and substantial statistical heterogeneity, meta-analysis was not undertaken for the outcomes of live birth and clinical pregnancy. For the outcomes of miscarriage and multiple pregnancy, the results of the meta-analysis of all

studies were similar to that of the primary analysis; endometrial injury appears to make little or no difference to the chance of either outcome.

Higher compared to lower degree of endometrial injury

Only one study was included in this comparison, which compared endometrial injury using two different instruments, a pipelle catheter and a Shepard catheter. As this study was small and suffered from numerous risks of bias (including lack of adequate allocation concealment or prospective trial registration), it was not included in the primary analyses. In the sensitivity analysis including all trials, all outcomes reported for this study were graded as very-low certainty, and as such we were not able to interpret the trial results.

There were no eligible studies for the comparison: different numbers of interventions.

Overall completeness and applicability of evidence

The included trials were relevant to the review question, assessing the effect of endometrial injury on the chance of live birth in women undergoing IVF. Most of the included trials reported the primary outcomes of live birth (or ongoing pregnancy) and miscarriage, and all studies reported the outcome of clinical pregnancy.

The included participants are likely to broadly represent women attending for IVF; including trials of women undergoing stimulated IVF cycles with fresh embryo transfer, and women undergoing frozen embryo transfer. Most of the included trials performed endometrial injury via pipelle biopsy in the luteal phase of the cycle preceding the IVF cycle; which is commonly undertaken in routine practice (Lensen 2016b). However, there were a number of trials employing interventions which may differ from standard practice, such as use of different instruments including a Novak curette (Karim Zadeh 2008; Karimzade 2010), Cook catheter (Sherif 2018), and scissors (Gurgan 2019); additionally, some trials conducted the procedure concurrently with hysteroscopy (Gurgan 2019; Narvekar 2010; Shohayeb 2012), or with granulocyte colony-stimulating factor instillation (Xu 2015). The included studies performed endometrial injury at various time points in relation to embryo transfer; from as distant as the follicular phase of the previous cycle to as proximal as the day of oocyte retrieval. Further, there was a large majority of trials conducted in the Middle-East (Turkey, Iran, Egypt) which may not be representative of the populations and IVF techniques used in other parts of the world; for example, many of the included trials reported mean number of embryos transferred >3, and consequently high multiple pregnancy rates.

Quality of the evidence

For the primary analyses which were restricted to studies at low risk of selection and other bias, the evidence was graded as moderate certainty for the outcomes of live birth, clinical pregnancy and miscarriage. The evidence was downgraded in these cases due to imprecision, as the confidence intervals were wide and consistent with a variation of possible effects including no effect and substantial benefit.

In the sensitivity analysis including studies with no high risk of bias, only one study was included (Mak 2017). All outcomes pertaining to this sensitivity analysis were graded as low quality due to downgrading for imprecision (as the study was small with consequently large confidence intervals) and indirectness (as the trial was undertaken in women undergoing frozen embryo transfer cycles only).

In the sensitivity analysis including all studies, the evidence was graded as low or very low due to downgrading for very serious risk of bias and inconsistency due to substantial statistical heterogeneity. The majority of the 38 included studies were associated with serious risk of bias. One particular concern was the lack of reported methods of randomisation or allocation concealment, introducing the risk that the studies were not indeed randomised trials. One trial reported that quote: "participants were randomly selected on the basis of their agreement to undergo endometrial biopsy" (Safdarian 2011) and another described the trial design as a quote: "prospective case-control study"(Guven 2014). Studies with unclear or high risk of bias for these domains have been associated with inflated (misleading) treatment effects (Wood 2008). Additionally, most included studies did not have adequate trial registration (27 studies), including nine studies that were not registered at all; despite all initiating recruitment after mandatory trial registration was introduced (De Angelis 2004). This introduces the potential for undisclosed selective outcome reporting, protocol changes, and other risks, including fraud (Roberts 2015).

A total of seven studies were available only as conference abstracts or clinical trial registrations. One research team supplied an unpublished full-text report of the trial (pending journal publication), and one further trial supplied the individual participant data for a trial which was terminated early and will not be published. Previous research has demonstrated a high degree of inconsistency between abstract reporting and full-text reporting, including examples of abstracts describing studies as randomised trials which are found not to have described true randomisation at full-text publication (Wu 2009). Many of the included studies did not blind participants and personnel to treatment allocation. Although studies implementing a sham were considered low-risk of bias, it remains unclear whether each of the various sham procedures used would have truly blinded participants to their allocation; and adequacy of the blinding was not reported in any trial. For example, it is conceivable that participants undergoing a sham procedure involving drying the cervix with gauze would be aware they had not undergone an intrauterine procedure, which is considerably more invasive. A number of studies terminated recruitment early due to unplanned interim analyses demonstrating futility or benefit, for difficulty recruiting, and for unknown reasons. Additionally, some studies reported inconsistent results within their publications. For example, the implantation rate (calculated as the number of sacs observed/number of embryos transferred) was not consistent with the reported multiple pregnancy rate and clinical pregnancy rate in some trials. Recent publications have provided evidence that trials in reproductive medicine, and specifically those evaluating endometrial injury, had extensive methodological issues which could bias the trial results, and that the data presented may not be consistent with properly conducted randomised trials (Li 2019).

Substantial statistical heterogeneity was observed when attempting to pool all trials for the outcomes of live birth and clinical pregnancy, as the treatment effects of included trials ranged from implausibly high benefit to significant harm. Therefore, meta-analysis was not undertaken in the sensitivity analyses for these outcomes.

Potential biases in the review process

The review authors tried to avoid publication bias by conducting comprehensive searches, including searches of ongoing trial registers and conference proceedings. While the aim of this approach is to identify all possibly eligible trials, it also results in the inclusion of trials which have poor trial methodology, have not been peer-reviewed, and for which limited methodology is available for our assessment of eligibility and risk of bias. After observing very serious risk of bias associated with many of the included studies, we made a post-hoc decision to restrict the primary analysis to studies at low risk of selection and other bias. These domains were selected because risk of selection bias is known to be associated with inflating treatment effects, and many of the studies presented with serious flaws, errors or inconsistencies which were captured under the domain of 'other' risk of bias. We also performed a sensitivity analysis including all studies, however meta-analysis was not possible for the outcomes of live birth and clinical pregnancy due to risk of bias and substantial heterogeneity.

Restructuring of the comparisons may also have introduced bias, as included studies were reclassified. Additionally, all of the review authors are investigators in clinical studies evaluating endometrial injury in IVF and which are included in this review.

Agreements and disagreements with other studies or reviews

Endometrial injury has been the topic of many studies and reviews. A number of reviews were conducted some time ago and therefore have not included the majority of studies identified in this review (Almog 2010; El-Toukhy 2012; Ko 2016; Panagiotopoulou 2015; Potdar 2012; Santamaria 2016; Zygula 2016b). There are at least a further four systematic reviews published in the last few years (Gui 2019; van Hoogenhuijze 2019; Vitagliano 2018; Vitagliano 2019).

In the recent review of endometrial injury in women with previous failure (Vitagliano 2018), 10 trials were included, missing only those that were conference abstracts (Karim Zadeh 2008), or published more recently (e.g. Pecorino 2018). This review also included one trial we elected to exclude for confusing results reporting (Singh 2015). The authors reported a higher probability of conception from endometrial injury, however graded the evidence as low or very low for most outcomes after downgrading for risk of bias and inconsistency. The authors also downgraded for indirectness however the rationale for this was not clear. Another recent review examined the evidence from trials of endometrial injury in women with at least one previous failure and included 10 trials (Sar-Shalom Nahshon 2018). In addition to excluding trials available only as abstracts, these reviewers included a trial in error as it was only pseudo-randomised i.e. not randomised (Matsumoto 2017). These reviewers reported benefit from endometrial injury but that the result was not statistically significant for the outcome of live birth.

In a review of women undergoing their first embryo transfer (Vitagliano 2019), seven trials were included. This review only missed studies that were abstracts (Hur 2012), had provided us data subgrouped into women with and without recurrent implantation failure (Gibreel 2015), informed us in author correspondence that all women were undergoing their first IVF cycle (Guven 2014), or were published more recently (e.g. Eskew 2018; Hilton 2019; Lensen 2019); one study we included was missed, which listed women with failed intracytoplasmic sperm injection (ICSI) as excluded (Sherif 2018). The authors report no difference in reproductive outcomes in women undergoing the injury or not, however they did not undertaken any GRADE assessment.

There are two recent reviews in the unselected population. One review excluded trials available only as abstracts, and only included trials performing the injury in the cycle prior to a stimulation (fresh) cycle (van Hoogenhuijze 2019). Therefore this review excluded a further four studies that we included in this review (Aflatoonian 2016; Guven 2014; Karimzade 2010; Mak 2017); and does not appear to have missed any further trials. Similarly, these reviewers were unable to pool the evidence for most planned subgroups due to high heterogeneity, commenting that many of the included trials were associated with a risk of bias and concluding that it remains unclear whether endometrial injury should be used prior to IVF. Another review conducted in the unselected population included randomised and non-randomised studies of endometrial injury or hysteroscopy and pooled all trials regardless of trial design. This review reported a significant benefit from endometrial injury (Gui 2019). After excluding non-randomised trials, the benefit was no longer present. This review failed to identify a number of trials included in the 2015 update of this Cochrane Review (Nastri 2015).

Overall, previous systematic reviews on this topic have largely focused on distinct subgroups of women undergoing IVF, and hence the results may differ from those presented here. Our review included conference abstracts, which is standard Cochrane methodology; however there are concerns that such reports may be prone to bias and may be misleading; such as not actually being randomised (Roberts 2016). Additionally, our review includes more recently reported trials; notably previous reviews have not included three large recent trials we include here (Metwally 2020; Lensen 2019; van Hoogenhuijze 2020). Despite these differences, the results and conclusions are broadly similar: that despite small studies suggesting possible benefit from endometrial injury, due to risk of bias and heterogeneity between studies, there is no sufficient evidence to recommend routine use of this procedure in practice.

Endometrial injury has also been investigated outside of IVF, in women trying to conceive from Intrauterine insemination (IUI) or intercourse - as this is the scope of another Cochrane Review, we do no touch on this topic here (Bui 2021).

AUTHORS' CONCLUSIONS

Implications for practice

The effect of endometrial injury on live birth and clinical pregnancy among women undergoing IVF is unclear. The results of the meta-analyses are consistent with an increased chance, no effect and a small reduction in these outcomes. We are therefore uncertain whether endometrial injury improves the chance of live birth or clinical pregnancy in women undergoing IVF. Endometrial injury does not appear to affect the chance of miscarriage. It is a somewhat painful procedure associated with a small amount of bleeding. In conclusion, current evidence does not support the routine use of endometrial injury for women undergoing IVF.

Implications for research

In this review we have included 38 trials investigating endometrial injury prior to an IVF cycle. Most of the trials conducted to date have been small and therefore lacked sufficient power to detect

clinically-relevant differences for clinical outcomes, and many were also associated with a high risk of bias. These trials have introduced significant heterogeneity into the evidence base, and consequently we have not been able to make clear sense of the variation in results reported for the sensitivity analyses. Given the large and heterogeneous evidence base presented here, and the large number of ongoing trials, initiating further trials on this topic is not encouraged.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aflatoonian 2016

Study characteristics	
Methods	RCT, 2 arms, 100 randomised Setting: Iran, research/clinical centre, one centre Study period: March 2015 to January 2016 (recruitment period unclear)
Participants	**Criteria related to previous IVF failure:** none **Inclusion criteria:** women indicated for frozen embryo transfer treatment, had one or more frozen embryo(s) and had a normal uterine cavity (confirmed by vaginal ultrasonography). **Exclusion criteria:** <40 years (assume error > 40), history of endocrine disorders (hypothyroidism, diabetes mellitus), intrauterine abnormality (uterine polyp, sub-mucosal fibroma, intrauterine adhesion) and severe endometriosis diagnosed by laparoscopy or endometrioma in ultrasound scanning.
Interventions	**Study group:** pipelle procedure once between days 21-23 of the cycle prior to the embryo transfer cycle **Control group:** no procedure
Outcomes	Reported in paper: ongoing pregnancy, clinical pregnancy, miscarriage, multiple pregnancy Obtained by author correspondence: -
Notes	Trial registration: IRCT2015101324512N1 (registered November 2015, retrospective registration) Additional concerns and comments: recruitment rate was high at approximately 14 patients per month. The first author is also the first author of an RCT which has been retracted for methodological issues, which may have been misrepresented (e.g. not a true RCT) (Aflatoonian 2013). The first author has published a large number of trials as first author recently (total of five RCTs as first author in the last

Aflatoonian 2016 *(Continued)*

10 years). Additionally, the implantation rates are not consistent with the clinical pregnancy and multiple pregnancy rates; which raises some concern about how the validity of the results.

Funding: the financial supporter was Research and Clinical Center for Infertility, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

Author correspondence: Attempted, however no response received

Publication: full-text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Paper states quote: "a computer-generated randomization table was created" but also that "93 consecutive subjects" were recruited, therefore unclear whether truly randomised
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding employed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only reporting objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears to be no attrition
Selective reporting (reporting bias)	High risk	Retrospective trial registration and not reporting live birth or adverse events such as pain/bleeding
Other bias	High risk	Trial registered retrospectively. Additionally, the implantation rates are not consistent with the clinical pregnancy and multiple pregnancy rates; which raises some concern about how the validity of the results.

Baum 2012

Study characteristics

Methods	RCT, 2 arms, 36 randomised Setting: Israel, academic research clinic, one centre Recruitment period: July 2006-June 2009
Participants	**Criteria relating to previous IVF failure:** yes, diagnosis of RIF (3 or more unsuccessful cycles of IVF-ET with good ovarian response in previous cycles) **Inclusion criteria:** age 18-41; scheduled for IVF with fresh embryo transfer on the next cycle **Exclusion criteria:** uterine malformation; presence of endometrioma; ultrasound evidence of hydrosalpinx

Baum 2012 *(Continued)*

Interventions	**Study group:** pipelle procedure undertaken twice, on days 9–12 and 21–24 of the spontaneous menstrual cycle preceding the IVF treatment cycle **Control group:** cervical pipelle was done by introducing the biopsy catheter into the cervix without scraping or taking a biopsy specimen, on the same days as above
Outcomes	Reported in paper: live birth, clinical pregnancy, miscarriage Obtained by author correspondence: -
Notes	Trial registration: NCT00411021 (registered Dec 2006, retrospective registration however was initiated post 2010) Additional concerns and comments: none Funding: none stated Author correspondence: attempted but no response received Publication: full-text

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed quote:"using a table of random numbers"
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were blinded by use of a cervical pipelle procedure.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only reporting objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears to be no attrition
Selective reporting (reporting bias)	High risk	Trial was registered 6 months into recruitment, however no outcomes listed. Live birth reported, however adverse events such as pain not reported.
Other bias	High risk	On the trial registration page the study authors planned to include 70 women in a cross-over trial; however in the published study, only 36 women were included and only 1 phase of the study was described. Reasons for the early stop are not stated. Additionally, the trial was registered late.

Berntsen 2020

Study characteristics

Methods	RCT, 2 arms, 229 randomised

Berntsen 2020 *(Continued)*

	Setting: Denmark, two public fertility clinics (only participants from one included in the analysis) Recruitment period: 2013 - 2018 (months not provided, recruitment period stated as 5 years)
Participants	**Criteria related to previous IVF failure:** yes, minimum one previous failed cycle **Inclusion criteria:** women were eligible if they had minimum one previous failed cycle and were planned to undergo their next IVF or ICSI cycle with fresh embryo transfer. Women between 18 and 40 years of age (both ages included) were included. **Exclusion criteria:** freeze-all cycles and frozen embryo transfers (FET) were excluded. Further, women were excluded if they had (i) BMI 35, (ii) known intrauterine pathology as cause of infertility, (iii) significant systemic disorders, (iv) ongoing infection (reproductive tract or systemic), (v) intrauterine abnormalities diagnosed during the trial hysteroscopy, or if they became spontaneously pregnant during the trial
Interventions	**Study group:** hysteroscopy and endometrial biopsy in the follicular phase of the preceding cycle, performed using 7 F forceps **Control group:** no procedure
Outcomes	Reported in paper: live birth, clinical pregnancy, miscarriage (defined as loss of a clinical pregnancy before 24 weeks, authors confirmed clinical pregnancy was defined as a positive pregnancy test) Obtained by author correspondence: the authors confirmed they did not measure pain or bleeding following the procedure.
Notes	Trial registration: NCT01743391 (registered Dec 2012, prospective registration) Additional concerns and comments: none Funding: Paper states quote: "No specific funding was sought for this study" Author correspondence: yes, undertaken with kristine.juul.hare.01@regionh.dk and sine.berntsen.01@regionh.dk. Publication: full-text. This poster was first discovered at the NFOG conference in Odense, 2018 (Poster ID ES27-0205), however there was no useable data in available in the poster.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The paper states quote: "participants were computer randomised using an online, third-party randomisation system and assigned...Randomisation was performed as a simple randomisation in a 1:1 ratio without using block randomisation or stratification...One physician was responsible for computer randomising all participants."
Allocation concealment (selection bias)	Low risk	A substantial imbalance in recruitment to each arm was observed (122 versus 107). No description provided in the paper however the authors informed us that quote:"The randomisation was performed in the program SAS. We used a logarithm where a physician (Dr Hare) typed the date of birth of the patient, this together with exact time – date, hour, minute and second, generated a number <1. All <0.5 were in group 1 (ESI group) all >0.5 were controls. All participants were only recruited/randomised once." Although it appears possible that the physician could have randomised women a second time to retrieve a different allocation, the authors also confirmed that the randomisation registered the patients Danish social security number and assigned a number based on the chronology of randomisation -

Berntsen 2020 *(Continued)*

		at the end of the study they checked that each patients social security number was only assigned a single randomisation event.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Trial was not blinded quote:"This was a randomised controlled trial (RCT) with no blinding of participants, investigators or health care personnel"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No subjective outcomes reported
Incomplete outcome data (attrition bias) All outcomes	High risk	It is stated that a number of women were excluded post-randomisation quote:"Freeze-all cycles and frozen embryo transfers (FET) were excluded. Further, women were excluded if they had... intrauterine abnormalities diagnosed during the trial hysteroscopy, or if they became spontaneously pregnant during the trial" The authors confirmed that these exclusions are all those documented within Figure 1. In total, there were 14 exclusions in the scratch arm and 3 in the control arm. This imbalance in exclusions may have impacted the analyses. Additionally, data from one of the two included centres was completely omitted due to clinic closure quote:"Data reported and analysed in this article are exclusively from the main centre at Copenhagen University Hospital, Hvidovre as the other fertility clinic (Holbaek) closed down during the study and the patients were lost to follow-up" and these are the 28 women (15 and 13) described as excluded in Figure 1.
Selective reporting (reporting bias)	Low risk	The trial was registered prospectively, and the listed outcomes are reported.
Other bias	Low risk	The trial was terminated early due to lack of funding, however this is not considered to cause bias

Eskew 2018

Study characteristics	
Methods	RCT, 2 arms, 100 randomised Setting: Washington University, St. Louis, USA, one centre Recruitment period: September 2013 - July 2017
Participants	**Criteria related to previous IVF failure:** no **Inclusion criteria:** women aged 18 or older undergoing a fresh or frozen embryo transfer. **Exclusion criteria:** third party reproduction, women undergoing a poor responder protocol, or women with a history of an abnormal uterine cavity
Interventions	**Study group:** endometrial biopsy with an endometrial pipelle in the luteal phase of the cycle prior to embryo transfer **Control group:** a sham biopsy (placement of pipelle in posterior fornix, withdraw plunger and "scratch" behind cervix 4 times- did not insert pipelle into cervix or uterus) during the luteal phase of the cycle prior to embryo transfer If patients were on oral contraceptive pills for their IVF cycle, the procedure was scheduled anytime during the last 7 days or up until 1 day after their pills were discontinued of the cycle prior to embryo transfer. If patients were not on oral contraceptive pills, patients were instructed to check for a lutein-

Eskew 2018 *(Continued)*

	ising hormone surge and the procedure was scheduled for 7–13 days following in the cycle prior to embryo transfer.
Outcomes	Reported in paper: live birth, clinical pregnancy, miscarriage Obtained by author correspondence: -
Notes	Trial registration: authors confirmed the study was not registered Additional concerns and comments: none Funding: NIH funding (5T32HD055172-09, UL1 TR002345) Author correspondence: yes, with Ashley Eskew (eskewa@wustl.edu) We noticed that the numbers of pregnancies and associated odds ratios were inconsistent in the text of the paper compared to the outcomes table. After contacting the authors we were reassured that the results in the outcomes table were correct; and the authors are contacting the journal to arrange a revision. Publication: full-text.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote:"randomization was performed using a computer-generated model with varied block lengths"
Allocation concealment (selection bias)	Low risk	Women were randomised using quote:"consecutively numbered sealed opaque envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Sham procedure implemented quote:"Both the patient and the clinician performing the embryo transfer were blinded to the randomization arm"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only reporting objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition: quote:"No patients were lost to follow up"
Selective reporting (reporting bias)	High risk	Authors confirmed trial was not registered, and adverse outcomes such as pain were not reported
Other bias	High risk	Trial stopped early for futility, only after observing challenges with recruitment. Stopping on the basis of O'Brien and Fleming 1979 rule means that the data available for meta-analysis give a biased effect estimate. Additionally the trial not registered.

Frantz 2019

Study characteristics

Methods	RCT, 2 arms, 191 randomised

Frantz 2019 *(Continued)*

	Setting: France, three centres Recruitment period: February 2010 - July 2014
Participants	**Criteria related to previous IVF failure:** yes, first or second IVF attempt **Inclusion criteria:** 18-38 years of age; primary or secondary infertility; regular menstrual cycles; follicle-stimulating hormone (FSH) ≤ 12 IU/L; signed informed consent **Exclusion criteria:** had participated to in oocyte donation program, presented a BMI > 35, had hydrosalpinx, uterine deformations, uterine fibroids (≥4 and the largest > 5 cm), abnormal gynaecological bleeding of unknown origin, or ongoing vaginal infection, had been pre-treated with oestrogen–progesterone or estradiol
Interventions	**Study group:** the biopsy is realised with a Pipelle de Cornier, moving the pipelle in and out while twisting, twisting the pipelle to cover an angle of 360° and making several "in and out" cycles to collect a complete sample of the endometrium. Performed between Day 20 and Day 24 of the cycle preceding ovarian stimulation **Control group:** no intervention
Outcomes	Reported in paper: ongoing pregnancy, clinical pregnancy, miscarriage, multiple pregnancy, pain, bleeding Obtained by author correspondence: -
Notes	Trial registration: NCT01064193 (registered Feb 2010, registered prospectively) Additional concerns and comments: none. Funding: Ministère de la Santé Français (Programme Hospitalier de Recherche Clinique 2009) Author correspondence: yes, brief correspondence with sandrine.frantz@chu-bordeaux.fr Publication: full-text.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Qquote:"The randomization sequence was generated using SAS Software...with a 1:1 allocation using random block sizes of 4 and 6" therefore adequate sequence generation
Allocation concealment (selection bias)	Low risk	Quote:"Randomization was...performed using a centralized web-based service"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was used. Additionally, there were a substantial number of women in the intervention arm who did not undergo the endometrial scratch (n = 25 of 98).
Blinding of outcome assessment (detection bias) All outcomes	High risk	The outcome of pain and adverse events were self-reported by participants who were not blind to their treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears only one women was lost to follow-up

Frantz 2019 *(Continued)*

Selective reporting (reporting bias)	Low risk	Trial was registered prospectively and all outcomes reported
Other bias	High risk	The study was quote:"stopped prematurely in July 2014 after an unplanned interim analysis" and "This analysis was prompted by the tendency towards lower pregnancy rates observed in the ES arm"

Gibreel 2015

Study characteristics	
Methods	RCT, 2 arms, 387 women randomised Setting: Egypt, academic and private clinics, 3 centres Recruitment period: January 2011 - June 2012 (provided by author correspondence)
Participants	**Criteria relating to previous IVF failure:** yes, at least one previous IVF failure **Inclusion criteria:** younger than 40 years of age with **Exclusion criteria:** women who were described as poor responders after previous IVF treatment (produced fewer than 3 oocytes or had their cycles cancelled because of poor follicular growth); women with known endocrinopathy; women undergoing tubal disconnection for hydrosalpinx; history of endometrial curettage within 3 months of the study; fibroids and other uterine factors (polyps, adhesions)
Interventions	**Study group:** pipelle procedure twice between days 21 and 26 of the cycle before the IVF index cycle and after initiation of the GnRHa in long agonist protocols **Control group:** placebo procedure using the uterine sound inserted into the cervix until the internal os on the same days of the cycle, as in women in the intervention group When the pipelle or the sound could not be introduced, a hysteroscopy was performed at the second appointment, in both groups
Outcomes	Reported in paper: live birth, clinical pregnancy, miscarriage, multiple pregnancy Obtained by author correspondence: -
Notes	Trial registration: NCT01245309 (registered Nov 2010, registered prospectively) Additional concerns and comments: recruitment rate is approximately 22 participants per month, however across three centres this is not deemed to be particularly high. Funding: university funding Author correspondence: yes, Ahmed Gibreel is a co-author of this Cochrane Review and the included trial Publication: full-text.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Paper states quote:"Randomization was performed through a computer generated tables of random numbers"

Gibreel 2015 *(Continued)*

Allocation concealment (selection bias)	High risk	Quote:"Women were asked to pick an opaque sealed envelope on the day of start of pituitary down-regulation" as the envelopes were not numbered this is graded as high risk
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Paper states quote:"Women were blinded to their allocation in the trial while physicians were not blinded". Women in the control arm underwent an endometrial sound procedure.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only reporting objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 dropouts in total, 3 in one arm and 2 in the other arm
Selective reporting (reporting bias)	Low risk	Trial was registered prospectively and all outcomes reported
Other bias	Low risk	-

Gurgan 2019

Study characteristics	
Methods	RCT, 2 arms, 305 randomised Setting: Turkey, private fertility centre, one centre Recruitment period: May 2015 - July 2017 (confirmed by author correspondence)
Participants	**Criteria related to previous IVF failure:** yes, the failure to achieve a clinical pregnancy after the transfer of at least four good-quality embryos in a minimum of three fresh or frozen cycles to a woman under the age of 40 years **Inclusion criteria:** under the age of 40 and follicle-stimulating hormone (FSH) levels ≤15 IU/mL, and meeting the above RIF condition **Exclusion criteria:** congenital uterine anomalies, patients with Asherman's syndrome, patients with uterine cavity distorted by myoma or endometrial polyps, patients with confirmed endometriosis or endometrioma and patients with BMI of <18.5 and >29.9, endometrium thickness of less than 7 mm in the cycle before the cycle
Interventions	**Study group:** Endometrial injury on the 10-12th day of late follicular phase in the preceding cycle through office hysteroscopy. Endometrial injury was performed without energy modality (i.e. with scissors). Endometrial injury was performed first on the fundus by cutting into the endometrium (without injuring the myometrium) transversally. Later, three or four vertical incisions were performed 0.5 cm apart each other, on the anterior and posterior walls of the uterus, 1-1.5 cm away from the fundus and one cut for each lateral wall. Also: standard gynaecological surgical procedures were used to treat recognized pathology **Control group:** no procedure
Outcomes	Reported in paper: live birth, clinical pregnancy, multiple pregnancy, miscarriage Obtained by author correspondence: -

Gurgan 2019 *(Continued)*

	Authors confirmed pain and bleeding were not collected.
Notes	Trial registration: NCT03748238 (registered Nov 2018, registered retrospectively) Additional concerns and comments: one of the trial authors (Makrigiannakis) is the first author of a retracted study, which appears to have been retracted for duplication (Makrigiannakis 2010); the implication of this is unclear. Funding: authors confirmed the study did not receive any specific funding Author correspondence yes, undertaken with muberranamli@hotmail.com Publication: full-text. A conference abstract was initially identified and the authors provided a report of the trial pending the full publication, and the full-text paper has now been published.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote:"randomized using a computer-generated random number sequence (1:1 simple randomization)"
Allocation concealment (selection bias)	Unclear risk	No description. Correspondence undertaken with the authors and it appears that no allocation concealment was in place quote: "Our computer program was very basic. Our numbers were given by turns 0 and 1. So it wasn't hidden and it was possible to see the next allocation if we check computer at that time"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was employed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only objective outcomes reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Three women in the injury group and 9 women in the control group were excluded for refusing their allocation. There was also an imbalance in the number of women with cancelled or failed IVF cycles: 13 in the injury group and 28 in the control group - which could lead to a higher pregnancy rate in the injury group under intention-to-treat. Additionally, 13 women in the injury group were excluded post-randomisation if uterine pathology was detected during the hysteroscopy quote:"Standard gynaecological surgical procedures were used to treat recognised pathology and any patients with surgical intervention other that endometrial injury were excluded from the study."
Selective reporting (reporting bias)	High risk	Registered retrospectively and only listing biochemical pregnancy as an outcome. Live birth reported, however adverse events such as pain not reported. The manuscript states "No hysteroscopy-related adverse events were reported" but it is unclear whether they measured pain and bleeding.
Other bias	High risk	Trial registered retrospectively

Guven 2014

Study characteristics	
Methods	RCT, 2 arms, 124 randomised Setting: Turkey, academic clinic, one centre Recruitment period: September 2010 - April 2011
Participants	**Criteria related to previous IVF failure:** yes, women were undergoing their first IVF cycle (as per author correspondence) **Inclusion criteria:** age < 35; history of primary infertility; normal responder (antral follicle count of 5 to 10 in 1 ovary at early follicular phase); grade I or II embryos for transfer **Exclusion criteria:** endocrinopathies; any systemic disease; history of neoplasm; high risk for or history of ovarian hyperstimulation syndrome; use of any concurrent medication; failure to proceed to follicle retrieval; severe male infertility requiring testicular sperm aspiration; Mullerian tract anomalies; history of endometrial instrumentation or surgery within 1 month of the study; fibroids and other uterine factors (polyps, adhesions); lack of agreement to undergo endometrial biopsy during the stimulation cycle
Interventions	**Study group:** endometrial injury was performed on day 3 of the menstrual cycle following down regulation; the scratching was done in 2 defined (anterior and posterior) portions of the uterine cavity under sterile conditions with the use of a biopsy catheter (Gynetics 4164 Probet Pipella, HD Aksu Medical, Ankara, Turkey) **Control group:** ***n*** o intervention
Outcomes	Reported in paper: live birth, clinical pregnancy, miscarriage Obtained by author correspondence: -
Notes	Trial registration: NCT01851876 (registered May 2013, registered retrospectively) Additional concerns and comments: trial recruited 124 women in 8 months from 1 centre (16 per month), which is a high recruitment rate for such a short recruiting window. Funding: unclear Author correspondence: yes, undertaken with the first author drsuleymanguven@yahoo.com Publication: full-text.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Trial registration describes study as non-randomised. Described in paper as quote: "prospective case–control study" and also as an RCT "Women were allocated at random (sealed envelopes) to the intervention group or the control group" author correspondence confirmed the trial was an RCT with computer-assisted randomisation
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes were used, unclear if SNOSE
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was employed

Guven 2014 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only objective outcomes reported
Incomplete outcome data (attrition bias) All outcomes	High risk	The eligibility criteria include having grade I or II embryos to transfer and no 'failure to proceed to follicle retrieval' which are post-randomisation exclusions as the women in the intervention arm underwent endometrial injury prior to follicle retrieval. It is unclear how many women were excluded for these reasons.
Selective reporting (reporting bias)	High risk	Trial registered retrospectively and adverse outcomes such as pain not reported
Other bias	High risk	Trial registered retrospectively.

Hilton 2019

Study characteristics	
Methods	RCT, 2 arms, 51 participants Setting: Canada, three centres Recruitment period: May 2013 to May 2015
Participants	**Criteria related to previous IVF failure:** yes, first or second IVF cycle **Inclusion criteria:** with or without ICSI; age 18–39 years; BMI 18–35 kg/m2 ; evaluation of uterine cavity (hysterosalpingogram, sonohysterogram, hysteroscopy) performed in the preceding 24 months; early follicular phase (day 2 or 3) serum FSH evaluated in the preceding 6 months; use of a long gonadotropin-releasing hormone agonist or antagonist protocol; and documented LH surge 9–11 days before enrolment for patients not pretreated with the oral contraceptive pill or use of the pill for ≥ 10 days at the time of enrolment. **Exclusion criteria:** previously enrolled in this study; had prior early follicular phase follicle-stimulating hormone level ≥ 12 IU/L; previous poor ovarian response (defined as prior IVF cycle cancelled for poor response or≤ 4 oocytes retrieved); IVF for preimplantation genetic diagnosis or fertility preservation, diabetes mellitus or uncontrolled thyroid disease; abnormal uterine cavity; untreated hydrosalpinx; any contraindication to endometrial biopsy, or if they had office hysteroscopy or other uterine procedure planned or performed during the cycle preceding IVF stimulation; or planned on using surgically retrieved sperm.
Interventions	**Study group:** a single endometrial biopsy performed 5-10 days prior to the start of gonadotropins in a standard IVF cycle **Control group:** no intervention
Outcomes	Reported in paper: [ive birth, clinical pregnancy, miscarriage Obtained by author correspondence: -
Notes	Trial registration: NCT01983423 (registered Nov 2013, registered retrospectively by only 6 months) Additional concerns and comments: none Funding: Unrestricted Educational Grant from Ferring Inc. (Canada) Author correspondence: Undertaken with JHavelock@pacificfertility.ca and Kimberly.Liu@sinaihealthsystem.ca

Hilton 2019 *(Continued)*

	Publication: full-text.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors described quote: "The SAS System for Windows was used generate randomization numbers that were accessed electronically using an encrypted web-based randomization system"
Allocation concealment (selection bias)	Low risk	As per the above description, allocation was concealed until the point of randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study described as quote:"open-label"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only objective outcomes reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears to be no attrition, this was confirmed by study authors
Selective reporting (reporting bias)	Low risk	Trial registered six months after initiating recruitment and all listed outcomes reported
Other bias	Low risk	Trial stopped early when only 51/332 intended participants recruited. Recruitment was closed due to difficulty recruiting, which is not itself considered a risk of bias.

Hur 2012

Study characteristics

Methods	RCT, 2 arms, 59 randomised Setting: South Korea, Maria Fertility Hospital, one centre Recruitment period: no description
Participants	**Criteria related to previous IVF failure:** yes, first IVF cycle only **Inclusion criteria:** all patients were under 35 years old, day 3 follicle-stimulating hormone level were below 10 IU/L. **Exclusion criteria:** infertility cause of uterine factor, severe male factor, and severe endometriosis were excluded.
Interventions	**Study group:** endometrial biopsy was done with a biopsy catheter (pipelle de cornier, France), performed only one time on starting day of stimulation. **Control group:** no procedure
Outcomes	Reported in paper: clinical pregnancy

Hur 2012 *(Continued)*

	Obtained by author correspondence: -
Notes	Trial registration: authors confirmed trial was not registered Additional concerns and comments: none Funding: no description Author correspondence: yes, correspondence undertaken with Dr Yeonhee Ka (miriuh@daum.net) and Dr Hur (cyhur68@gmail.com). Authors provided the poster that was presented at the conference. Publication: abstract only (and poster)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors confirmed quote:"patient allocation was made by computerized randomization"
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was implemented
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only reported objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only abstract available therefore difficult to assess level of attrition
Selective reporting (reporting bias)	High risk	Trial was not registered and important outcomes such as live birth and adverse events not reported
Other bias	High risk	Trial published as abstract only with limited detail, and further information not obtained from author correspondence. Trial not registered.

Inal 2012

Study characteristics

Methods	RCT, 2 arms, 100 randomised Setting: academic setting, Turkey Study period: January 2008-March 2009 (unclear if recruitment period or entire study period)
Participants	**Criteria related to previous IVF failure:** yes, failed to conceive during 1 or more cycles of IVF and embryo transfer (ET) **Inclusion criteria:** women considered to be good responders to hormonal stimulation; age between 25 and 36 years

Inal 2012 *(Continued)*

	Exclusion criteria: hydrosalpinx; thrombophilia; submucous myoma and factors found to have a negative impact on implantation
Interventions	**Study group:** 2 consecutive endometrial biopsies at 1-week intervals during the luteal phase of the non-transfer cycle, when on Gonadotropin-releasing hormone agonist for downregulation. Endometrial biopsy was performed with a biopsy catheter (Pipelle de Cornier, Prodimed, Neuilly-en-Thelle, France) introduced through the cervical os and rotated within the uterine cavity 3-4 times after withdrawal of the piston. Antibiotics were administered after the procedure **Control group:** no intervention
Outcomes	Reported in paper: live birth, clinical pregnancy, miscarriage Obtained from author correspondence: -
Notes	Trial registration: believed to be: NCT01340560 (registered Apr 2011, registered retrospectively) Additional concerns and comments: Implantation and clinical pregnancy rates appear inconsistent; similar implantation rates reported in each arm (31% versus 35%) however clinical pregnancy rates significantly different (34% versus 60%); no obvious explanation. Funding: quote:"This study has no financial support" Author correspondence: yes, undertaken Publication: full-text.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Paper states quote:"The randomization was based on a computer generated random numbers"
Allocation concealment (selection bias)	Unclear risk	No description provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was employed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only objective outcomes reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears to be no attrition
Selective reporting (reporting bias)	High risk	Unclear if registered, and important outcomes such as adverse events not reported
Other bias	High risk	Trial registered retrospectively. There is an apparent inconsistency in the implantation and pregnancy rates reported, which are similar per arm for implantation rate but significantly different for clinical pregnancy rates.

Izquierdo Rodriguez 2020

Study characteristics	
Methods	RCT, 2 arms, 352 randomised Setting: Spain, one private IVF centre (ProcreaTec Fertility Clinic) Recruitment period: January 2017 to October 2018
Participants	**Criteria relating to previous IVF failure:** no **Inclusion criteria:** women undergoing egg donation, Included patients' age ranged between 18 and 50 years, and all had normal uterine cavity, assessed by 2D transvaginal ultrasound. Patients with endometrial polyps were only included if polypectomy was performed at least 2 months before the treatment cycle. **Exclusion criteria:** severe male factor (less than 2 million sperm per mL) or if they presented any factor interfering with embryo implantation, such as uterine abnormalities (uterine fibroids classified as 0–2 FIGO stage, Müllerian malformations, or severe adenomyosis) or unilateral or bilateral hydrosalpinx; BMI over 35 kg/m2, previous endometrial scratch or hysteroscopy (less than a month before the randomisation)
Interventions	**Study group:** Scratch performed 5 to 10 days before their period started and the endometrial preparation began. The scratch was carried out in an out-patient setting under abdominal ultrasound guidance. A speculum was inserted into the vagina and after cervix disinfection with an iodine solution, an endometrial biopsy catheter (Pipelle de Cornier,Laboratoire CCD, France) was inserted through the cervix into the uterine cavity. Once in the cavity, the catheter piston was partially removed to create a suction effect and the catheter was then moved back and forth and rotated 360° in order to scratch the four walls. **Control group:** no procedure
Outcomes	Reported in paper: live birth, clinical pregnancy, miscarriage, multiple pregnancy Obtained via author correspondence: the authors provided data subgrouped by women with/without recurrent implantation failure, which we have used in the subgroup analyses. The authors stated that quote:"3 patients were scratch was difficult, 6 patients who referred some mild pain and 9 patients that suffered from some spotting some days after the technique and before their period started" however that "there was not a specific questionnaire or scale to report pain or bleedings and not all patients were specifically asked just after the scratch. Since some data were obtained after the treatment, it was possible that this information was not 100% accurate, so that is why it was not included in our paper" and also we have not included it in this review for the same reasons.The authors also provided the results subgrouped by RIF nonRIF.
Notes	Trial registration: NCT03108157 (registered Apr 2017, registered 3 months retrospectively) Additional concerns and comments: recruitment rate is approximately 16 participants per month, which may be considered high for a trial recruiting over a period of only 22 months, however cannot on its own be considered a serious risk of bias. The authors suggested the recruitment rate may be higher than other studies owing to the wider inclusion criteria used in the study. The authors provided the live birth data among women with recurrent implantation failure, and the overall live birth rate in this group was 57% (81/143) which is relatively high for a recurrent implantation failure population, and was also higher than the women in the study without implantation failure, however the women in this study were receiving donated eggs. Funding: this work was fully supported by ProcreaTec Fertility Center. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors Author correspondence: yes, with Alexandra Izquierdo, izquierdo.alexandra@yahoo.es Publication: full-text.

Izquierdo Rodriguez 2020 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The paper states that quote:“The randomization chart was obtained by a web-based randomization program (randomization.com) using simple randomization. Patients were allocated to a treatment arm (group A—intervention arm, group B—control arm) and then received the instructions for their treatment protocol.”
Allocation concealment (selection bias)	High risk	There is no description of the randomisation process, however the authors confirmed that they quote:"used the software to obtain a long list of allocations and patients were included in consecutive order. If patients accepted the study, they were assigned to each group at the moment they accepted the treatment and dates, according to the list" and specifically that "we could see the next allocation" therefore allocations were not concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was used as the paper states quote:Blinding was not possible since patients in the study group received an intervention and those in control group did not (no placebo intervention was performed).”
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No subjective outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although in the paper it was not clear, we confirmed with the authors that there were no women lost to follow-up or withdrawn from the trial. The 5 women that appear to have been lost in Figure 1 had missing data for pregnancy complications and newborn information only.
Selective reporting (reporting bias)	Low risk	Trial was registered late, but only by 3 months, and all outcomes were collected. therefore rated as low-risk
Other bias	Low risk	-

Karimzade 2010

Study characteristics

Methods	RCT, 2 arms, 156 randomised Setting: Iran in an academic setting Recruitment period: June 2008 to January 2009
Participants	**Criteria related to previous IVF failure:** yes, participants were undergoing their first IVF cycle **Inclusion criteria:** age < 38 years; BMI > 19 kg/m^2 and < 30 kg/m^2; day 3 follicle-stimulating hormone < 12 mIU/ mL; triple-layer endometrium with thickness > 8 mm on the day of human chorionic gonadotrophin administration; normal ovarian response to stimulation (estradiol on the day of trigger between 500 and 3000 pg/mL and between 4 and 14 retrieved oocytes **Exclusion criteria:** any uterine anomaly such as myoma and endometrial polyp on USTV; endometrioma with a diameter > 3 cm; visible hydrosalpinges
Interventions	**Study group:** one endometrial injury procedure using Novak curette on the day of oocyte retrieval

Karimzade 2010 *(Continued)*

	Control group: no intervention
Outcomes	Reported in paper: ongoing pregnancy, clinical pregnancy. Miscarriage calculated as the difference between clinical and ongoing pregnancies. Obtained by author correspondence: -
Notes	Trial registration: NCT00846183 (registered Feb 2009, registered retrospectively) Additional concerns and comments: over a recruitment period of 8 months the researchers recruited 156 women (19.5 per month). This is a high recruitment rate for one centre. Three of the four authors are also authors of an RCT which has been retracted for methodological issues, which may have been misrepresented (e.g. not a true RCT) (Aflatoonian 2013). Funding: no description Author correspondence: attempted but no response received Publication: full-text.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer generated randomization method"
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was employed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only objective outcomes reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Four women were excluded from the analysis because they had bleeding on the day of planned embryo transfer and therefore embryo transfer was cancelled. It is a reasonable assumption that these four women did not conceive.
Selective reporting (reporting bias)	High risk	Trial was registered retrospectively and live birth not reported
Other bias	High risk	Quote:"because of significant lower pregnancy rates in the experimental group, the study was stopped sooner" it is not clear whether adequate stopping rules were used. Trial registered retrospectively. Three authors are also co-authors of a retracted paper.

Karim Zadeh 2008

Study characteristics

Methods	RCT, 2 arms, 160 randomised Setting: Iran in an academic setting

Karim Zadeh 2008 *(Continued)*

	Recruitment period: not described
Participants	**Criteria related to previous IVF failure:** yes, at least 2 prior implantation failures **Inclusion criteria:** at least 2 prior implantation failures **Exclusion criteria:** -
Interventions	**Study group:** Novak endometrial suction curettage during the secretory phase in a non-medicated cycle before IVF/ICSI **Control group:** no intervention
Outcomes	Reported in paper: Clinical pregnancy Obtained by author correspondence: -
Notes	Trial registration: does not appear to be registered Additional concerns and comments: one of the authors is an author on a paper which has been retracted for duplication, as it was very similar to another paper by the same author group in a different journal (Mohsenzadeh 2018). Funding: no description Author correspondence: - Publication: abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation was not described
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding employed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only objective outcomes reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It is unclear whether there was an attrition or dropout
Selective reporting (reporting bias)	High risk	Trial not registered and important outcomes such as live birth and adverse events not reported
Other bias	High risk	Published only as a conference abstract with limited detail; no further information could be retrieved from study authors. Trial not registered. Authors are also co-authors of a retracted paper.

Karimzadeh 2009

Study characteristics	
Methods	RCT, 2 arms, 115 randomised Setting: Iran in an academic setting Recruitment period: Unclear
Participants	**Criteria related to previous IVF failure:** yes, recurrent implantation failure (defined as 2 to 6 unsuccessful cycles of IVF-embryo transfer with previous transfer of at least 10 high-grade embryos without achievement of clinical pregnancy) **Inclusion criteria:** age between 20 and 40 years; no history of blood disease; **Exclusion criteria:** age > 40 years; poor response in previous cycles (defined as day 3 follicle-stimulating hormone > 10 IU mL or < 4 follicles on the day of trigger in previous cycle); uterine malformation; presence of endometrioma; ultrasound evidence of hydrosalpinx
Interventions	**Study group:** 1 endometrial injury procedure using Pipelle de Cornier on days 21-26 of spontaneous cycle **Control group:** no intervention
Outcomes	Reported in paper: clinical pregnancy Obtained by author correspondence: -
Notes	Trial registration: does not appear to be registered Additional concerns and comments: one of the authors is an author on a paper which has been retracted for duplication, as it was very similar to another paper by the same author group in a different journal (Mohsenzadeh 2018). Funding: Research and Clinical Center for Infertility, Shahid Sadoughi University of Medical Sciences. Author correspondence: attempted but no response received Publication: full-text.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Random selection to either group was performed by drawing a piece of paper from the bag containing equal number of printed paper for each method"
Allocation concealment (selection bias)	High risk	No description of any safeguards in place to ensure allocation concealment and prevent someone from replacing the paper and selecting another
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was employed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only objective outcomes reported

Karimzadeh 2009 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Nine women lost to follow-up in each arm (4 and 5)
Selective reporting (reporting bias)	High risk	Trial does not appear to have been registered and important outcomes such as live birth and adverse events not reported
Other bias	High risk	Trial not registered. Authors are also co-authors of a retracted paper.

Lensen 2019

Study characteristics	
Methods	RCT, 2 arms, 1364 randomised Setting: 13 academic/public hospital centres across five countries (New Zealand, Australia, UK, Belgium, Sweden) Recruitment period: June 2014 - June 2017
Participants	**Criteria related to previous IVF failure:** no **Inclusion criteria:** women planning IVF with their own oocytes (stimulated IVF cycle with planned fresh transfer, or frozen embryo transfer using stored embryos) **Exclusion criteria:** not planning an embryo transfer (e.g. fertility preservation or planned freeze-all cycles), had any contraindication to pipelle biopsy (e.g. vaginismus), or had undergone any disruptive intrauterine procedures within three months prior to commencing IVF, specifically: hysteroscopy, sonohysterogram, hysterosalpingogram, laparoscopy, surgically managed miscarriage or endometrial biopsy
Interventions	**Intervention**: single endometrial pipelle biopsy performed between day 3 of the menstrual cycle preceding the embryo transfer cycle and day 3 of the menstrual cycle for which embryo transfer is planned **Control**: no procedure
Outcomes	Reported in paper: live birth, clinical pregnancy, miscarriage, multiple pregnancy, pain, bleeding Obtained by author correspondence: -
Notes	Trial registration: ACTRN12614000626662 (registered June 2014, registered prospectively) Additional concerns and comments: none Funding: University of Auckland, New Zealand; the A+ Trust, Auckland District Health Board, New Zealand; the Nurture Foundation, New Zealand; and the Maurice & Phyllis Paykel Trust, New Zealand Author correspondence: yes, one of the investigators is an author on this Cochrane Review (s.lensen@auckland.ac.nz) Publication: full-text.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "An online, third-party, data collection and randomisation system was used... participant allocations were concealed within the system until the patient was randomised. Participants were randomised in a 1:1 ratio using block

Lensen 2019 *(Continued)*

		randomisation of two different sizes between 6 and 16 repeating in random order, stratified by recruiting site and by whether a fresh or frozen embryo transfer was planned"
Allocation concealment (selection bias)	Low risk	As above
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was used. A higher proportion of women in the endometrial injury arm underwent embryo transfer compared to women in the control arm; however there was no impact on the results after adjusting for this observation
Blinding of outcome assessment (detection bias) All outcomes	High risk	The outcome of pain during the procedure and bleeding were self-reported by participants who were not blind to their treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Minimal attrition: four women withdrew from the trial and the pregnancy outcome of one further women is unknown
Selective reporting (reporting bias)	Low risk	Trial was registered prospectively and the protocol published; all outcomes reported
Other bias	Low risk	-

Liu 2017

Study characteristics	
Methods	RCT, 4 arms, 142 randomised Setting: Beijing Obstetrics and Gynecology Hospital, China - one centre Recruitment period: February 2012 to November 2014
Participants	**Criteria related to previous IVF failure:** yes, patients were undergoing first IVF cycle **Inclusion criteria:** infertile women indicated for IVF treatment; ≤40 years of age; a normal uterine cavity demonstrated by saline infusion sonogram; basal follicle stimulating hormone (bFSH) <12 IU/L **Exclusion criteria:** endometrium with polyp or fibroid; hydrosalpinx; endometriosis.
Interventions	**Study group:** for patients in proliferative phase group, endometrial injury was performed between cycle day 10–12. For patients in luteal phase group, endometrial injury was performed 7–9 days after ovulation. The endometrial injury procedure was performed in a standard approach using a pipelle **Control group: p**ipelle catheter inserted through the cervix but no injury was performed to the endometrium (on either cycle days 10-12 or 7-9 after ovulation)
Outcomes	Reported in paper: live birth, clinical pregnancy, multiple pregnancy, miscarriage (provided in paper but numbers do not match the difference between live birth and clinical pregnancy, therefore miscarriage calculated based on this difference instead), pain, bleeding Obtained by author correspondence: -
Notes	Trial registration: ChiCTR-IOR-17011506 (registered May 2017, registered retrospectively) Additional concerns and comments: the outcomes of all clinical pregnancies are not known, for example there are 29 clinical pregnancies in the intervention group and 1 miscarriage, 1 ectopic and 25 live

Liu 2017 *(Continued)*

births; there is no description of the fate of the other two pregnancies. Additionally, there are two ectopics in total reported in Table 2 but only one in Table 4 - however only small numbers are involved.

Funding: the study was supported by the National Natural Science Foundation of China (81471520), Beijing Natural Science Foundation Project (5122015), and Project Training High-Level Medical Technical Personnel in the Health System in Beijing (2014–3-075).

Author correspondence: attempted but no response received (yingliubj@hotmail.com)

Publication: full-text.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "table of random numbers" was used
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A sham procedure was implemented which is considered likely to blind participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Subjective outcome of pain reported and participants were blind to their trial allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There appears to be no attrition, however the paper states that all randomised women underwent embryo transfer, which seems unlikely for all 142 women. It is possible that some women were excluded.
Selective reporting (reporting bias)	Low risk	Retrospective registration however live birth and adverse events reported
Other bias	High risk	Trial registered retrospectively. Additionally, the outcome of some pregnancies are not accounted for which questions the accuracy of the data.

Mackens 2020

Study characteristics

Methods	RCT, 2 arms, 200 randomised Setting: Belgium, one University Hospital. Recruitment period: April 2014 - October 2017 (confirmed with authors)
Participants	**Criteria related to previous IVF failure:** no **Inclusion criteria:** 18-40 years of age; fresh IVF/ICSI cycle; antagonist downregulation; signed informed consent **Exclusion criteria:** other known reasons for impaired implantation (i.e. hydrosalpinx, fibroid distorting the endometrial cavity, Asherman's syndrome, thrombophilia or endometrial tuberculosis); oocyte donation acceptors; frozen egg transfers; embryos planned to undergo embryo biopsy; BMI >35 or <18;

Mackens 2020 *(Continued)*

	women already recruited for another trial on medically assisted procreation during the same cycle; women who have previously enrolled in the trial; those unable to comprehend the investigational nature of the proposed study
Interventions	**Study group:** endometrial biopsy was performed on Days 6 to 8 of ovarian stimulation with a Pipelle de Cornier® (Laboratoire CCD, France). The device was introduced into the uterus until slight resistance from the fundus was felt after which the piston was withdrawn and the device rotated through 360° as it was moved up and down for four times **Control group:** no intervention
Outcomes	Reported in paper: live birth, clinical pregnancy, miscarriage, bleeding, pain Obtained by author correspondence: -
Notes	Trial registration: NCT02061228 (registered Feb 2014, registered prospectively) Additional concerns and comments: the trial authors conduct a large number of RCTs run at this single academic centre. However, all RCTs were found to be staggered and conducted in non-overlapping populations. Funding: 'Fonds Wetenschappelijk Onderzoek' (FWO, Flanders, Belgium, 11M9415N, 1524417N). Author correspondence: yes, with Shari Mackens Shari.Mackens@uzbrussel.be and Samuel dos Santos Ribeiro, samueldsribeiro@gmail.com Publication: full-text.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	As per paper quote: "randomization sequence and allocation was appointed using a computer-generated randomization list with a 1:1 allocation"
Allocation concealment (selection bias)	Low risk	Quote:"concealment was ensured with sequentially numbered, opaque, sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding and subjective outcomes reported: pain and bleeding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 women withdrew in the control group
Selective reporting (reporting bias)	Low risk	Trial was registered prospectively and reports all review outcomes originally planned. Some additional outcomes such as premature birth and low birth weight not reported, but not review outcomes
Other bias	High risk	The quote:"trial was terminated prematurely following the second interim analysis after the recruitment of 200 patients due to safety concerns (specifically, a potentially increased risk of miscarriage in the intervention arm)" and there does not appear to be any statistical adjustment made for these multiple interim analyses

Maged 2018

Study characteristics	
Methods	RCT, 2 arms, 300 randomised Setting: Kasr Al Ainy IVF unit in Cairo, Egypt - one centre Study period: 1 January 2016 to 31 March 2017 (unclear if this is recruitment period)
Participants	**Criteria related to previous IVF failure:** yes, first time ICSI **Inclusion criteria:** candidates for ICSI, were to undergo ICSI for the first time, and met the following inclusion criteria: aged younger than 40 years, the follicle-stimulating hormone (FSH) level measured on the third day of a natural cycle was less than 10 IU/L, the serum prolactin level was normal, and uterine cavity abnormality was excluded by hysteroscopy or hysterosalpingography. **Exclusion criteria:** abnormal endocrine function (e.g. abnormal thyroid or adrenal function), ovarian cysts, hydrosalpinx, endometrial polyps, male partner with azoospermia, and ICSI performed for preimplantation genetic diagnosis
Interventions	**Study group:** endometrial injury was induced by performing endometrial aspiration in the mid luteal phase of the cycle immediately preceding the scheduled IVF treatment, using a Pipelle catheter **Control group:** no procedure
Outcomes	Reported in paper: clinical pregnancy, miscarriage, multiple pregnancy Obtained by author correspondence: - Although the authors report clinical pregnancies and miscarriages before 12 weeks, it was not appropriate to calculate Ongoing pregnancy as the difference between these two numbers as it was unclear whether all participants 12 week status was confirmed as either Ongoing or not.
Notes	Trial registration: NCT02660125 (registered 17 Jan 2016, appears to be registered in the same month as recruitment initiated however recruitment period unclear) Additional concerns and comments: the recruitment rate is high; the study is stated to have been conducted within 15 months (Jan 2016-March 2017) and was submitted to the journal in May 2017. Women were followed to the stage of clinical pregnancy (6-8 weeks following endometrial scratch), therefore 300 women were recruited within 13 months = 20-23 women per month. It appears the trial may have been registered a few weeks late. Authors were contacted to request ethics approval letter and were unable to produce this. We wrote to the ethics office and received no response. The first author has co-authored a total of 20 RCTs within 10 years, 17 of which as first author. This might be considered an impressive and possibly improbable rate of RCT publications. The study reports an unusually high multiple pregnancy rate; the average number of embryos replaced was approximately 1.4 per woman (428 embryos transferred to 300 women), yet of the clinical pregnancies 51% were multiples - this is much higher than other studies included in this review that have similar or higher numbers of embryos replaced. The clinical pregnancy rate was determined on ultrasound 4 weeks after embryo transfer, however the implantation rate is reported as being captured by ultrasound at 14 days after embryo transfer; at such an early gestation it is unlikely that gestational sacs would be visible. Lastly, the methods state that the antagonist protocol was used for women with a previous history of OHSS, however all women were undergoing their first ICSI cycle. Funding: authors confirmed no funding used Author correspondence: yes, with Ahmed Maged (prof.ahmedmaged@gmail.com) Publication: full-text.
Risk of bias	

Maged 2018 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote:"automated web-based randomization system"
Allocation concealment (selection bias)	Low risk	No description in paper, however authors confirmed during correspondence that the randomisation was tied to the participant trial ID and subversion of allocation was not possible
Blinding of participants and personnel (performance bias) All outcomes	High risk	paper states quote:"neither the participants nor the clinicians were masked to group assignment"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only objective outcomes reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears to be no attrition
Selective reporting (reporting bias)	Low risk	Trial registered prospectively and all outcomes are reported
Other bias	High risk	There are a number of concerns about this trial, including the high recruitment rate, large number of other RCTs published recently by the first author, and an unexpectedly high multiple pregnancy rate.

Mak 2017

Study characteristics	
Methods	RCT, 2 arms, 229 randomised Setting: Hong-Kong, research/academic institution, one centre Study period: March 2013 to April 2016 (unclear if recruitment period or whole study period)
Participants	**Criteria related to previous IVF failure :**no **Inclusion criteria:** scheduled for frozen embryo transfer (FET) cycles using non-donor oocytes, normal ovulation and were deemed suitable for natural-cycle FET **Exclusion criteria:** any uterine anomaly or pathology such as endometrial polyps, endometriomas larger than 4 cm or hydrosalpinx.
Interventions	**Study group:** pipelle procedure performed once in the mid-luteal phase of the cycle preceding the embryo transfer cycle**Control group:** endocervical manipulation with pipelle, performed once in the mid-luteal phase of the cycle preceding the embryo transfer cycle
Outcomes	Reported in paper: live birth/ongoing pregnancy, clinical pregnancy, miscarriage, multiple pregnancy Obtained by author correspondence: -
Notes	Trial registration: ChiCTRTRC-12002389 (registered Aug 2012, registered prospectively)

Mak 2017 *(Continued)*

	Additional concerns and comments: None
	Funding: None stated
	Author correspondence: minimal correspondence with jennifermak@cuhk.edu.hk
	Publication: full-text.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote:"computer generated random numbers"
Allocation concealment (selection bias)	Unclear risk	The random numbers were quote:"concealed in opaque envelopes" unclear if SNOSE
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Sham procedure used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only reporting objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	8/115 and 5/114 women withdrew from the trial (small numbers)
Selective reporting (reporting bias)	Low risk	Registered prospectively and all outcomes reported
Other bias	Low risk	-

Merriam 2017

Study characteristics

Methods	RCT, 2 arms, 129 randomised (only including each women's first randomisation)
	Setting: USA, one centre
	Recruitment period: Jan 2014 - Dec 2017 (provided by authors)
Participants	**Criteria related to previous IVF failure:** no
	Inclusion criteria: all patients undergoing embryo transfer who are in the cycle prior to their embryo transfer
	Exclusion criteria: patients not undergoing embryo transfer, Known pregnancy, Active pelvic infection, Known endometrial hyperplasia or cancer, Inability to tolerate endometrial catheter placement, Severe cervical stenosis, patients who will receive operative hysteroscopy in the cycle prior to embryo transfer
Interventions	**Study group 1:** endometrial injury performed with pipelle on days 21-27 in the cycle prior to the IVF cycle

Merriam 2017 *(Continued)*

	Study group 2: endometrial injury performed by a Shepard insemination catheter on days 21-27 in the cycle prior to the IVF cycle
Outcomes	Reported in paper: live birth, pain Obtained by author correspondence: live birth, clinical pregnancy and pain data provided for the 129 women randomised. Miscarriage calculated as the difference between clinical pregnancy and live birth.
Notes	Trial registration: NCT04363879 (registered April 2020, registered retrospectively) Additional concerns and comments: none Funding: The protocol states quote: "This study does not have a budget. There will be no charge to the patient for the endometrial activation because the physicians have agreed to donate their time, and the procedures will be done in-office" Author correspondence: yes, undertaken with Brad.Hurst@atriumhealth.org and goldrick@uthscsa.edu Publication: abstract only This study was presented as a conference abstract in 2017. The authors have since registered the trial and updated the 'Study Results' tab with information and a Statistical Analysis Plan. Information from all of these sources, including correspondence with the authors, has been used for the purposes of this review. During author correspondence it was discovered that the study had permitted re-randomising of women. Therefore we have used data in this review from only each women's first randomisation - and a total of 129 women were randomised.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The authors confirmed that a quote:"1:1 ratio of codes went into envelopes which were then shuffled and chosen at random to randomize patients"
Allocation concealment (selection bias)	High risk	The authors confirmed that quote:"Envelopes were plain envelopes without writing on them", these do not meet the SNOSE criteria and are therefore considered high-risk
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was used.
Blinding of outcome assessment (detection bias) All outcomes	High risk	The outcome of pain during the procedure was self-reported by participants who were not blind to their treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	Women were excluded for not undergoing the endometrial scratch or an embryo transfer. Of 129 women, 13 were excluded (8 in the pipelle arm, 5 in the Shepard catheter arm) which is 10% of the 129 women recruited, therefore this is considered high-risk
Selective reporting (reporting bias)	High risk	The trial was registered retrospectively and important outcomes such as bleeding and miscarriage were not reported
Other bias	High risk	Only an abstract is available. Although the authors provided additional data and clarification via email, it remains possible that important methodological detail that may result in bias has not been disclosed. Additionally, the trial was registered retrospectively.

Metwally 2020

Study characteristics	
Methods	RCT, 2 arms, 1048 randomised Setting: UK, 16 IVF clinics Study period: June 2016 – Oct 2019 (unclear if recruitment period or entire study period)
Participants	**Criteria relating to previous IVF failure:** yes, women undergoing their first IVF cycle **Inclusion criteria:** (extracted from protocol) 1. Women expected to be aged between 18 and 37 years (inclusive) at time of egg collection. 2. First-time IVF with or without ICSI treatment using the antagonist or long protocol only. 3. Expected to receive treatment using fresh embryos. 4. Expected good responders to treatment, with: a. Ovulatory menstrual cycle b. Normal uterine cavity c. Expected good ovarian reserve **Exclusion criteria:** (extracted from protocol) 1. Previous trauma/surgery to the endometrium (e.g. resection of submucous fibroid, intrauterine adhesions). 2. Body mass index (BMI) of 35 kg/m2 or greater. 3. Known grade 4 (severe) endometriosis. 4. Currently participating in any other fertility study involving medical/surgical intervention. 5. Expected to receive protocols other than antagonist or long (e.g. ultra long protocol). 6. An endometrial scratch (or similar procedure, e.g. endometrial biopsy for the collection of natural killer cells) is planned. 7. Previously randomised into this trial.
Interventions	**Study group:** Endometrial Scratch (ES) performed in the mid luteal phase prior to IVF/ICSI. The procedure is performed with a pipelle or similar. **Control group:** no procedure
Outcomes	Reported in paper: live birth, clinical pregnancy, miscarriage. Information regarding pain was provided in a box plot during the oral presentation, however it was not possible to determine the mean and SD from this presentation. Obtained from author correspondence: -
Notes	Trial registration: ISRCTN23800982 (registered May 2016, registered prospectively) Additional concerns and comments: none Funding: NIHR (UK) Author correspondence: yes, limited correspondence undertaken with Robin Chatters (r.chatters@sheffield.ac.uk) Data reported in the trial abstract was slightly different to that reported in the oral presentation; however the authors did not answer our questions, we therefore used the abstract data. For the same reason, the methodological information relating to the trial was extracted from the supplied study documents (protocol, SAP etc) as the authors did not answer our questions. Publication: abstract only (and oral presentation viewed at ESHRE 2020)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The protocol states quote: "The randomisation schedule will be generated by Sheffield CTRU prior to the start of the trial; access to the schedule will be limited only to the trial statistician. The randomisation sequence will be computer generated and stratified by site and protocol (antagonist or long protocol). Random permuted blocks of variable size will be used to ensure enough participants are allocated evenly to each arm of the trial at each site"

Metwally 2020 *(Continued)*

Allocation concealment (selection bias)	Low risk	The protocol states "Research staff at recruiting centres will be unable to access the randomisation sequence and will use a web-based computer system with restricted access rights to enter participant details; randomisation outcome will then be revealed"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was used. Also it was observed that a higher proportion of women in the endometrial injury arm underwent double embryo transfer compared to women in the control arm.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome of pain during the procedure were self-reported by participants who were not blind to their treatment allocation, however this data was not available for inclusion in this review.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information available about the numbers of women lost to follow-up or withdrawn
Selective reporting (reporting bias)	Unclear risk	Although the study protocol was registered prospectively, only an abstract is available and therefore it is not possible to assess whether all registered outcomes have been/will be reported
Other bias	Low risk	Only an abstract is available and the trial team refused to answer our questions by email, however sufficient information was available and therefore this is not seen to constitute a high risk of bias.

Narvekar 2010

Study characteristics	
Methods	RCT, 2 arms, 100 randomised Setting: India, private fertility clinic, one centre Recruitment period: May 2007 to July 2008
Participants	**Criteria relating to previous IVF failure:** yes, women with at least 1 previous failure **Inclusion criteria:** good responders in the previous IVF cycle (development of at least 4 good-quality embryos); ≤ 37 years **Exclusion criteria:** endometrial tuberculosis in the past; intramural fibroid distorting the endometrial cavity/submucous myoma; Asherman's syndrome; evidence of hydrosalpinx
Interventions	**Study group:** pipelle procedure conducted twice: once at the time of hysteroscopy on days 7-10, and again on days 24-25 (of the cycle before IVF) **Control group:** hysteroscopy on days 7-10 of the cycle before IVF
Outcomes	Reported in paper: live birth, clinical pregnancy, miscarriage, multiple pregnancy Obtained from author correspondence: -
Notes	Trial registration: trial does not appear to be registered Additional concerns and comments: none Funding: none stated

Narvekar 2010 *(Continued)*

Author correspondence: yes, undertaken with corresponding author (sachnar@rediff.com)

Publication: full-text.

Numbers of previous attempts were 2.3 ± 0.52 and 2.5 ± 0.7, so the study was classified in the subgroup 'Two or more previous failures'

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers were used
Allocation concealment (selection bias)	Low risk	Sealed and consecutively numbered opaque envelopes were used
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was employed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only objective outcomes reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	It does not appear there was any attrition or loss to follow-up
Selective reporting (reporting bias)	High risk	The trial does not appear to have been registered, and important outcomes such as adverse events not reported
Other bias	High risk	Trial not registered.

Nastri 2013

Study characteristics

Methods	RCT, 2 arms, 158 randomised Setting: Brazil, academic research centre, one centre Recruitment period: June 2010 to March 2012
Participants	**Criteria relating to previous IVF failure:** no **Inclusion criteria:** all women undergoing ART with planned fresh embryo transfer aged < 38 years **Exclusion criteria:** -
Interventions	**Study group:** pipelle procedure performed once 7 to 14 days before the start of ovarian stimulation **Control group:** sham procedure performed at the same time. This procedure comprised drying of the cervix with no insertion of any instrument into the cervix or womb
Outcomes	Reported in paper: live birth, clinical pregnancy, miscarriage, multiple pregnancy, pain, bleeding

Nastri 2013 *(Continued)*

	Obtained by author correspondence: -
Notes	Trial registration: NCT01132144 (registered May 2010, registered prospectively) Additional concerns and comments: none Funding: this study was funded by two Brazilian official government research foundations: CNPq (direct funding (process number 473475/2010-3) and research scholarship) and CAPES (PhD scholarship). Author correspondence: yes, two of the authors are authors on this review (CO, WPM) Publication: full-text.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Paper states quote:"computer generated random sequence of numbers in blocks of 30 (each block having 15 numbers assigned to intervention and 15 to control"
Allocation concealment (selection bias)	Low risk	Paper states quote:"The allocation was sealed in consecutively numbered opaque envelopes and an envelope was assigned as the participant entered the study; however, sealed envelopes were only opened just before the procedure, to ensure allocation concealment"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Sham procedure employed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Sham procedure implemented therefore outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no attrition or loss to follow-up
Selective reporting (reporting bias)	Low risk	Trial was registered prospectively and all outcomes reported
Other bias	High risk	The trial was terminated early for a positive effect

Olesen 2019

Study characteristics

Methods	RCT, 2 arms, 304 randomised Setting: Denmark, 4 public fertility clinics Recruitment period: February 2014 - December 2017
Participants	**Criteria related to previous IVF failure:** yes, one or more prior implantation failures, **Inclusion criteria:** eligible patients were IVF or intracytoplasmic sperm injection

Olesen 2019 *(Continued)*

	patients with one or more prior implantation failures, despite top-quality embryo or blastocyst (19) transfer(s). Further inclusion criteria were regular menstrual cycle (28–32 days), age 18–40 years, and a body mass index (BMI) 18–32 kg/m2 **Exclusion criteria:** women with congenital uterine abnormalities, fibroids, or polyps were excluded, as were women with suspected hydrosalpinges and adenomyosis.
Interventions	**Study group:** Scratching was performed, using a Pipelle de Cornier (Laboratoires Prodimed) in the luteal phase before ovarian stimulation at cycle day 18–22 for the intervention group. The scratching was carried out with the patient lying in a lithotomy position and was performed once in each quadrant of the endometrium. **Control group:** no procedure
Outcomes	Reported in paper: live birth, clinical pregnancy, miscarriage, multiple pregnancy. Obtained by author correspondence: authors confirmed the multiple pregnancy rates reported in the per-protocol analysis also applied to the ITT analysis. The authors also confirmed that the paper reports a mistake in the miscarriage rates reported, which should be 8 in the scratch arm and 13 in the control arm. The paper reports that quote: "There were no uterine infections, bleeding, or adverse events reported, besides a short pain during the endometrial scratching procedure" however it is not clear how many women this occurred in.
Notes	Trial registration: NCT01963819 (registered Oct 2013, registered prospectively) Additional concerns and comments: none Funding: Health Research Fund of the Central Denmark Author correspondence: yes, undertaken with Mia Olesen miaolsen@rm.dk Publication: full-text.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Paper states quote: "participants were randomized into blocks of 10 for each participating clinic in a ratio of 1:1, according to an Internet-based randomization list"
Allocation concealment (selection bias)	Low risk	Paper states that the quote:"randomization list that was sealed in consecutively numbered opaque envelopes" and the authors confirmed that study staff did not know the block size which was used
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was used quote:"The study was nonblinded, and no sham procedure was carried out in the control group"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Although the authors reported that some women experienced a short pain during the scratch; this data was not available in a useable format for this review.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears to be no attrition, this was confirmed by the authors

Olesen 2019 *(Continued)*

Selective reporting (reporting bias)	Low risk	Trial was registered prospectively and all outcomes were reported
Other bias	Low risk	-

Pecorino 2018

Study characteristics	
Methods	RCT, 2 arms, 80 randomised Setting: Italy, one centre Recruitment period: unclear
Participants	**Criteria related to previous IVF failure:** yes, at least two previous failed ICSI or FIVET (failed implantation) **Inclusion criteria:** between 25- 37 years, primitive or secondary infertility, normal thickness and endometrial ultrasound pattern, defined as absence of intracavitary disease (fibroids, polyps, etc.), with no anamnestic severe deep endometriosis, good quality of seminal fluid of partner and negative anamnesis for relevant diseases, negative genetic, metabolic and infective evaluation. **Exclusion criteria:** as above
Interventions	**Study group:** endometrial scratching was performed by a dedicated team (2 operators only) during luteal period, between 5 and 10 days before menstruation. Pipelle used. **Control group:** sham procedure using an embryo-transfer catheter introduced along the cervix inside the uterine cavity.
Outcomes	Reported in paper: clinical pregnancy, pain, bleeding Obtained by author correspondence: pain mean and SD (intervention group mean pain 5.6, SD 1.2, control group: mean 4.0, SD 0.9), multiple pregnancy (only reported in one arm in paper)
Notes	Trial registration: authors confirmed the trial was not registered Additional concerns and comments: the implantation rate does not appear to have been calculated correctly, however this does not have a bearing on the outcomes included in this review. Funding: Authors state the trial was funded "by the Hospital" Author correspondence: yes, undertaken with Basilio Pecorino eliopek@gmail.com Publication: full-text.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The paper states quote:"performed a randomized unblinded controlled trial (RCT) in a ratio of 1:1" correspondence with the authors confirmed "computerized random numbers" were used
Allocation concealment (selection bias)	Low risk	No description in the paper however correspondence with authors confirmed each quote: "patient was inserted after login in a Crf software for randomization. Crf returned the modality of scratching for each patient: scratch or con-

Pecorino 2018 *(Continued)*

		trol" and that "there was no way to foresee the next allocation before randomization" which suggests adequate allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Control group underwent a sham procedure however the authors also describe the study as unblinded quote:"performed a randomized unblinded controlled trial". Authors confirmed that patients were blind to their trial allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Subjective outcome of pain reported and participants were blind to their trial allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Paper states quote:"All of recruited patients completed reproductive procedures including embryo transfer" therefore no attrition
Selective reporting (reporting bias)	High risk	Study was not registered and important outcomes such as Live birth not reported
Other bias	High risk	Trial not registered

Polanski 2015

Study characteristics	
Methods	RCT, 2 arms, 160 randomised Setting: UK, Nurture Fertility, one centre Recruitment period: January 2013 to July 2014
Participants	**Criteria related to previous IVF failure:** no **Inclusion criteria:** women younger than 49 years with history of primary or secondary infertility undergoing fresh IVF/ICSI treatment or frozen embryo replacement cycle **Exclusion criteria:** non-ovulatory cycle; absent uterus; uterine instrumentation within previous 3 menstrual cycles; women in the oocyte donation programme
Interventions	**Study group:** endometrial biopsy procedure using Pipelle endometrial sampler (Pipelle de Cornier, Laboratoire CCD, Paris, France) or Wallace/Wallach endometrial sampler as an alternative device; ultrasound performed before the procedure. Procedure performed on cycle day luteinizing hormone (LH) +7 to LH+9 of the cycle directly preceding commencement of down-regulation before IVF or ICSI treatment **Control group:** no intervention
Outcomes	Reported in paper: Clinical pregnancy, miscarriage Obtained by author correspondence: live birth, multiple pregnancy, pain (binary), bleeding
Notes	Trial registration: NCT01882842 (registered Jun 2013, registered 5 months retrospectively) Additional concerns and comments: none Funding: the University of Nottingham and Nurture Fertility through local research funds. Author correspondence: yes, undertaken with Nick.Raine-Fenning@nurturefertility.co.uk and lucas.polanski@hotmail.com

Polanski 2015 *(Continued)*

This trial was included in the previous version of this review with ongoing/interim data (Polanski 2014). The study is now finished, and was presented at a conference in 2015 but has not yet been published in full; further details and outcomes were provided by author correspondence.

Publication: abstract only (and authors provided a full-text manuscript, which has not been published).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote:"computer generated random code using random permuted blocks of randomly varying size was used to allocate participants" from author correspondence
Allocation concealment (selection bias)	Low risk	Patient details were entered into an online randomisation tool, author correspondence confirmed randomisation only revealed after entering the participants details into the computer program
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was used
Blinding of outcome assessment (detection bias) All outcomes	High risk	The outcome of pain during the procedure and bleeding were self-reported by participants who were not blind to their treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	The authors informed us that six women in intervention arm and four in control arm excluded either because withdrew from trial or did not attend for treatment, small numbers - these are only small numbers.
Selective reporting (reporting bias)	Low risk	Registered approximately 6 months into recruitment, however all important outcomes including live birth reported.
Other bias	Low risk	The paper is described as a pilot study. Despite a formal power calculation requiring 766 women the study recruited only 160 women due to available timeframe (18 months) and a recruitment rate of 50%. Additionally, the results are only available as an abstract. The authors provided a manuscript for this paper however it has not been published in full. The study was registered late by 5 months. These concerns were not deemed sufficient to constitute a high risk of other bias.

Safdarian 2011

Study characteristics

Methods	RCT, 2 arms, 100 randomised Setting: Iran, hospital, one centre Study period: July 2008 to March 2009 (unclear if recruitment period or whole study period)
Participants	**Criteria relating to previous IVF failure:** no **Inclusion criteria:** 20 to 39 year-old infertile women who were referred to the fertility centre

Safdarian 2011 *(Continued)*

	Exclusion criteria: women older than 39 years of age; follicle-stimulating hormone > 11; endometriosis; hypothalamic amenorrhoea; azoospermic male
Interventions	**Study group:** pipelle procedure on day 21 menstrual cycle preceding IVF cycle, with use of contraceptive pill before IVF-embryo transfer treatment **Control group:** no procedure
Outcomes	Reported in paper: clinical pregnancy Obtained by author correspondence: -
Notes	Trial registration: IRCT201008154572N1 (registered Sep 2011, registered retrospectively) Additional concerns and comments: across an apparent 9-month recruitment period, trial team recruited 11 women per month - which is a reasonably high rate, however not on its own a serious concern. Funding: this project was financially supported by Infertility Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran. Author correspondence: Emails sent to corresponding author (shmovahedy@razi.tums.ac.ir) but no reply received Publication: full-text.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Computerised; participants were randomly selected on the basis of agreement to undergo endometrial biopsy expressed in a written informed consent before the start of the IVF cycle. This wording suggests the allocation was based on the participants agreement or preference, therefore unclear whether truly randomised.
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding employed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only reporting objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Does not appear to be any attrition
Selective reporting (reporting bias)	High risk	Trial was registered retrospectively and only reported clinical pregnancy, not live birth or any adverse events.
Other bias	High risk	Trial registered retrospectively.

Shahrokh-Tehraninejad 2016

Study characteristics	
Methods	RCT, 2 arms, 120 randomised Setting: Iran, hospital/fertility clinic, 2 centres Recruitment period: January 2013 to December 2014
Participants	**Criteria related to previous IVF failure:** yes, previous history of at least two failure of IVF/ICSI cycles **Inclusion criteria:** age < 40 years, presence of at least 4 embryos with good quality (grade 1), normal uterus in hysterosalpingography (HSG), sonography, hystrosonography or hysteroscopy, and at least 7mm endometrium thickness at suppository progesterone administration day. All patients had anatomically normal uterus cavity without any pathology like hyperplasia, malignancy, or endometritis in uterus. No one had received oral contraception agents or gonadotropin-releasing hormone before FET cycle. **Exclusion criteria:** submucosal, intramural, and subserous al myoma greater than 5 cm, endometrioma equal to or greater than 3 cm, hydrosalpinx, bilateral obstruction of tube, less than 3-4 embryos, endometrial tuberculosis, previous history of tuberculosis treatment, Asherman's syndrome, BMI > 30 kg/m2, active vaginal or cervical infection, and underlying diseases like diabetes or systemic lupus erythematous.
Interventions	**Study group:** pipelle procedure day 21 of the cycle preceding the frozen embryo transfer cycle **Control group:** no procedure
Outcomes	Reported in paper: live birth, clinical pregnancy, miscarriage Obtained by author correspondence: - (Authors stated during correspondence that all pregnancies were single however this seems unlikely given the average number of embryos transferred was 3, therefore this data was not used. Authors also stated that pain and bleeding were captured and "there was not any problem" - however this data was not used as unclear how actively this information was captured)
Notes	Trial registration: IRCT201311065181N12 (registered Oct 2015, registered retrospectively) Additional concerns and comments: of 130 women assessed for eligibility, 120 were randomised - which is a higher enrolment rate than usual, but not on its own a source of serious concern. Funding: None stated Author correspondence: emailed the corresponding author with some success (fedyeh_hagh@yahoo.com) Publication: full-text.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Paper states quote: "Random selection for each method was performed by drawing a piece of printed paper from the plastic bag containing of equal number. Numbers of 1-59 for treatment group and 60-120 for control group were selected and By visiting each patient, randomly a number was out of plastic and according to the number, the group was selected."
Allocation concealment (selection bias)	High risk	No description of any safeguards in place to ensure allocation concealment and prevent someone from replacing the paper and selecting another

Shahrokh-Tehraninejad 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding employed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only objective outcomes reported
Incomplete outcome data (attrition bias) All outcomes	High risk	It is unclear whether any participants were excluded as one of the inclusion criteria appear to relate to a characteristic that would only be known after randomisation (7 mm endometrial thickness on progesterone administration day). It was not possible to confirm this with the authors.
Selective reporting (reporting bias)	High risk	No valid trial registration, and important outcomes such as adverse events not reported
Other bias	High risk	Trial registered retrospectively.

Sherif 2018

Study characteristics	
Methods	RCT, 2 arms, 60 randomised Setting: Ain-Shams University Hospital, Egypt - one centre Recruitment period: no description
Participants	**Criteria related to previous IVF failure:** yes, women with previous failed ICSI were excluded **Inclusion criteria :**age between 25 and 30 years old, BMI between 20 and 30, Cause of infertility either tubal causes, ovulatory causes, unexplained causes **Exclusion criteria:** endometriotic patients, Male factor of infertility, Uterine cavity abnormalities, previous failed ICSI, hydrosalpinx and pyosalpinx.
Interventions	**Study group:** single induced injury was done on the posterior endometrium 1 cm to 2 cm from the fundus by using modified Cook catheter, on day 6 of the ICSI cycle **Control group:** no procedure
Outcomes	Reported in paper: clinical pregnancy Obtained by author correspondence: -
Notes	Trial registration: PACTR201701001968212 (recruitment period unclear however stated to be conducted between 2015-2017 on trial registry, therefore unclear whether registration was prospective or not but likely retrospective) Additional concerns and comments: none Funding: No description Author correspondence: attempted but no reply received (ahmedsherif@med.asu.edu.eg) Publication: full-text.
Risk of bias	

Sherif 2018 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was achieved by a computer generated randomization table (Research Randomizer Version 4.0 software)".
Allocation concealment (selection bias)	Unclear risk	No description (trial registration says opaque envelopes used, however this is not described in the paper)
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding employed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only objective outcomes reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears to be no attrition
Selective reporting (reporting bias)	Unclear risk	All outcomes from trial registration page are reported, but unclear whether registration was prospective
Other bias	High risk	Trial does not appear to have been registered prospectively. There was a significant difference in fertilisation rate in favour of the interventional group 83 (63–100) versus 67 (47–83) in the control group (P = 0.020), which would create bias in favour of the intervention arm.

Shohayeb 2012

Study characteristics	
Methods	RCT, 2 arms, 210 randomised Setting: Egypt and Saudia Arabia, academic and private settings, two centres Recruitment period: June 2009 to July 2011 (provided by the authors)
Participants	**Criteria relating to previous IVF failure:** yes, women with history of 2 or more failed ICSI cycles despite transfer of high-quality embryos **Inclusion criteria:** normal thin endometrium (< 5 mm) on day 4 of menstruation; younger than 39 years of age **Exclusion criteria:** abnormal endometrial cavity (submucous myoma encroaching on the cavity, endometrial polyp, intrauterine synechia); septate or bicornuate uterus diagnosed by transvaginal ultrasound or by hysterosalpingography
Interventions	**Study group:** hysteroscopy and endometrial scraping were done once in the follicular phase at days 4–7 in the cycle preceding the embryo transfer cycle using a Novak curette **Control group:** hysteroscopy was done without endometrial scraping
Outcomes	Reported in paper: live birth, clinical pregnancy, miscarriage Obtained by author correspondence: multiple pregnancy

Shohayeb 2012 *(Continued)*

Notes	Trial registration: not registered (confirmed by authors) Additional concerns and comments: the second author has published 7 RCTs in the last 10 years, including 5 as first author. Trial recruitment completed July 2011 and the article was submitted for publication in December 2011 and reports on live birth; there does not appear to be sufficient time for completion of follow-up etc within this window. Funding: no funding (confirmed by authors) Author correspondence: yes, undertaken with corresponding author (waleed_elkhyat@yahoo.com) Publication: full-text.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Paper states quote: "The patients were randomly distributed using random number tables"
Allocation concealment (selection bias)	Low risk	Paper states quote: "the treatment allocation was done using closed sealed envelope by an assigned nurse before the hysteroscopy" and authors confirmed "envelope was numbered sequentially and was opaque brown" therefore SNOSE
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although the description of the procedures suggest the procedure may have blinded participants to their allocation, it is not specifically stated that they were blinded and it is unclear whether participants were informed of their trial allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only objective outcomes reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears to be no attrition or loss to follow-up
Selective reporting (reporting bias)	High risk	Trial was not registered, and important outcomes such as adverse events not reported
Other bias	High risk	Trial not registered. There are concerns about the rate of RCT publication from the authors, and improbable timelines for recruitment, follow-up and publication.

Tang 2020

Study characteristics

Methods	RCT, 2 arms, 220 women Setting: China, two hospitals Study period: October 2017 - February 2018 (unclear if recruitment period or whole study period).
Participants	**Criteria related to previous IVF failure:** yes, quote: "at least two or more previous implantation failures"

Tang 2020 *(Continued)*

	Inclusion criteria: patients indicated for frozen–thawed embryo transfer (ET), with serum progesterone level < 1.2 ng/mL on the third day of the menstrual cycle, at least two or more previous implantation failures, normal morphology of uterine cavity **Exclusion criteria:** history with pelvic surgery history, history with difficult ET and aged more than 40 years; intrauterine abnormality (severe adhesions, uterine polyp, submucosal fibroma), BMI > 27 kg/m2, hydrosalpinx, endometriosis and receiving oral contraception drugs recently.
Interventions	**Study group:** endometrial soft scratch on the third day of the menstrual cycle proceeding frozen–thawed ET cycle, using a pipelle catheter. It was confirmed with the authors that the endometrial scratch was performed in the same cycle as the FET cycle. **Control group**: no procedure
Outcomes	Reported in paper: live birth, clinical pregnancy, miscarriage, multiple pregnancy Obtained by author correspondence: The results in the paper left 12 clinical pregnancies unaccounted for (i.e. not ending in miscarriage or live birth). The authors confirmed there was: 1 stillbirth, 1 ectopic, 1 miscarriage and 2 events meeting the criteria for live birth (showing signs of life) in the EI arm, and 2 ectopics, 2 stillbirths, 1 termination and 2 events meeting the criteria for live birth (showing signs of life) in the control arm. We therefore amended the live birth data to reflect these 4 additional live births. Additionally, although the paper states that quote: "potential complications were carefully monitored and no significant vaginal bleeding, fever, abdominal pain and other complications were found in EI group" the authors confirmed these were not actively measured or collected, therefore we did not use this data.
Notes	Trial registration: ChiCTR-IPR-17014013 (registered Dec 2017, registered two months retrospectively/3 months before the end of the study) Additional concerns and comments: Trialists appear to have recruited 220 women in 5 months (44 recruits per month, 22 per centre); an exceptionally high recruitment rate, especially of participants with recurrent implantation failure. The authors confirmed this recruitment rate is correct, and that the trial was conducted at a high productivity clinic, during a time of especially high productivity due to the timing of a Spring Festival and cultural preference to conceive at this time. The live birth rate in the study was 41% (91/220) which is relatively high for a recurrent implantation failure population. Funding: quote: "The study was supported by HeFei Municipal Health Planning Commission in 2017 (hwk2017yb009), Key Research and Development Project of AnHui Province(1701a0802171), Key Talents of Maternal and Child Health in Jiangsu Province (FRC201715) and Science Technology Innovation Project of Suzhou (SS201702)" Other publications: None Author correspondence: Yes undertaken with Zhixia Tang: tzx1999@163.com Publication: full-text.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The paper states quote: “Randomization was done simply using sealed envelopes before undergoing EI” and the authors replied that "the random numbers are generated from to the random number table"
Allocation concealment (selection bias)	Low risk	The paper states quote: “Randomization was done simply using sealed envelopes before undergoing EI.” Unclear if the envelopes were sequentially numbered, opaque and sealed, however the authors replied that the envelopes were "light-tight" and that the "cover of the envelope is marked with

Tang 2020 *(Continued)*

		serial numbers, like 1, 2, 3" therefore the envelopes appear to meet SNOSE criteria.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: “After randomization, physicians and participants were aware of the trail-group assignments” not blinded therefore high risk
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only objective outcomes were reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was no attrition, as confirmed with the authors. 20 women (10 in each arm) were excluded from the analysis, however these were all women who had a cancelled embryo transfer, and these women are therefore assumed not to have conceived
Selective reporting (reporting bias)	Low risk	Trial was registered in December 2017 and recruitment started in October 2017, only 3 months late, and all planned outcomes reported, therefore low-risk.
Other bias	High risk	The trial was registered late, only 2-3 months before completing recruitment. Additionally, the recruitment rate for the study was very high, and the live birth rate was also higher than might be expected for this population.

TK 2017

Study characteristics	
Methods	RCT, 2 arms, 111 randomised Setting: India, one centre (a private university) Recruuitment period: April 2008- April 2015 (confirmed with authors that this is the recruitment period).
Participants	**Criteria related to previous IVF failure:** yes, quote: "at least one previous failed cycle with minimum of two good quality embryos (cleavage or blastocyst stage) transferred in an earlier attempt" **Inclusion criteria:** age 21-38; follicle-stimulating hormone < 10 mL IU/mL ; BMI 20–29 kg/m^2 **Exclusion criteria:** poor responders (< 3 oocytes in a previous IVF cycle); local uterine pathology (adhesions, polyp, etc); severe endometriosis, gross adenomyosis; uterine malformations; systemic disease such as autoimmune disorders
Interventions	**Study group:** pipelle biopsy performed twice in the luteal phase of the month before the start of controlled ovarian stimulation **Control group:** no procedure
Outcomes	Reported in paper: live birth, clinical pregnancy, miscarriage, multiple pregnancy. Obtained from author correspondence: authors reported that no participant experienced clinically significant bleeding or pain following the procedure, however as this was not actively recorded we did not use this data in the review
Notes	Trial registration: CTRI/2013/04/003564 (registered Apr 2013, registered retrospectively)

TK 2017 *(Continued)*

	Additional concerns and comments: none Funding: quote: "No funding support" Other publications: none Author correspondence: yes, with Mohan Kamath (dockamz@gmail.com) Publication: full-text. This trial was included in the previous version of this review with ongoing/interim data (Aleymma 2013). The study is now finished and published.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Paper states quote: "Computer generated sequence was generated in blocks of ten".
Allocation concealment (selection bias)	Low risk	Paper states quote: "Eligible women... were randomly allocated... by opening consecutively numbered sealed opaque envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was employed. The total dose of FSH administered was higher in the control group; however this is unlikely to significantly impact the outcomes.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only objective outcomes reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Appears to be no attrition
Selective reporting (reporting bias)	Low risk	Retrospective trial registration, however all review outcomes were reported
Other bias	High risk	Trial stopped before reaching recruitment target due to slow recruitment and because quote: "stronger evidence emerging in favour of endometrial injury, it became ethically challenging to continue the trial" which itself is not considered a risk of bias. However, the authors also performed unblinded interim analysis (these data were included in previous version of the review) and made no adjustment for this in the final analysis. Additionally, the trial was registered retrospectively.

van Hoogenhuijze 2020

Study characteristics

Methods	RCT, 2 arms, 946 randomised Setting: the Netherlands, 8 academic and 24 general hospitals Recruitment period: January 2016 to July 2018
Participants	**Criteria related to previous IVF failure:** yes, all participants had one previous IVF/ICSI failure

van Hoogenhuijze 2020 *(Continued)*

	Inclusion criteria: women were eligible if they had undergone 1 full IVF/ICSI cycle with at least 1 embryo transfer without achieving a clinical pregnancy and were planning a new fresh IVF/ICSI cycle. Inclusion criteria were regular indication for IVF/ICSI, age between 18-44 years, primary or secondary infertility and a normal transvaginal ultrasound. **Exclusion criteria:** endometriosis grade 3/4, untreated uni- or bilateral hydrosalpinx, previous endometrial scratching, untreated endocrine abnormalities, intermenstrual blood loss, previous Caesarean section with niche-formation and intracavitary fluid visible on ultrasound, increased risk of intra-abdominal infection, oocyte donation cycles or preimplantation genetic testing
Interventions	**Study group:** single endometrial scratch in the menstrual cycle prior to the start of stimulation for IVF/ICSI. The scratch was performed either in the mid-luteal phase of a natural cycle or in a cycle with hormonal contraceptives, using an endometrial biopsy catheter **Control group:** no procedure
Outcomes	Reported in paper: live birth, clinical pregnancy, miscarriage, pain, bleeding Obtained from author correspondence: multiple pregnancy
Notes	Trial registration: NTR 5342 (registered July 2015, registered prospectively) Additional concerns and comments: none Funding: Dutch organisation for funding of healthcare research ZonMW. Author correspondence: yes, undertaken with N.E.vanHoogenhuijze@umcutrecht.nl and H.Torrance@umcutrecht.nl Publication: Full-text.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Paper states quote: "Participants were randomised 1:1 to the intervention or control group by a centrally-located, non-centre-stratified, web-based randomisation programme using randomly permuted blocks, with block size varying randomly between two and four."
Allocation concealment (selection bias)	Low risk	Supplementary file provided with the paper described adequate processes for randomisation and allocation concealment quote: "Allocation concealment was ensured by the web-based randomisation programme, as the persons who registered participants for randomisation could not see how many participants had already been randomised or what their allocation was"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was used. A higher proportion of women in the endometrial injury arm underwent embryo transfer compared to women in the control arm; however there was no impact on the results after adjusting for this observation
Blinding of outcome assessment (detection bias) All outcomes	High risk	The outcome of pain during the procedure and bleeding were self-reported by participants who were not blind to their treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 7 women in the scratch arm and 13 in the control arm did not have primary outcome data: 5 women in the scratch arm and 8 in the control arm were excluded from the analyses. Of these, 2 in the scratch arm, and 7 in the control arm were excluded for not returning a hard copy of their consent form. The refusal to return the form could have resulted from knowledge of trial allocation and therefore be different across the two arms, however the numbers

van Hoogenhuijze 2020 *(Continued)*

		are relatively low. An additional 2 in the scratch and 5 in the control arm were lost to follow-up for the primary analyses. However, together these numbers are small and unlikely to impact the primary outcome.
Selective reporting (reporting bias)	Low risk	The trial was registered prospectively and the authors provide a transparent supplementary file of all the changes made since study inception/registration, which are minor. All measured outcomes are reported.
Other bias	Low risk	-

Wolff 2018

Study characteristics	
Methods	RCT, 2 arms, 19 randomised Setting: private fertility centre, USA - one centre Recruitment period: unclear
Participants	**Criteria related to previous IVF failure:** yes, one or more previous implantation failures **Inclusion criteria:** women age 18-37, one or more previous implantation failures with autologous fresh or frozen blastocyst transfer, undergoing fresh autologous IVF cycle, no other current uterine (i.e.: uterine fibroids, polyps), haematological, or genetic causes for infertility and implantation failure, one or more good quality blastocyst(s) available for transfer **Exclusion criteria:** those unable to comprehend the investigational nature of the proposed study, positive pregnancy test, possible causes for impaired implantation (systemic disease, endometriosis, ultrasound evidence of current hydrosalpinx, uterine polyps, uterine myomas (fibroids), uterine cavity malformations or Asherman's syndrome), poor responders defined as follicle-stimulating hormone >12 on day 3 or less than 4 follicles on a previous IVF cycle, BMI >30 or <18
Interventions	**Study group:** endometrial pipelle (Endocell, Wallach, Orange, Connecticut) inserted gently through the cervix into the uterus. Two passes will be performed with the pipelle catheter. For each pass the catheter will be rotated and scraped 4 times, once in each quadrant. The procedure is performed in the month prior to the IVF cycle, and it appears in the Protocol provided that the procedure is performed twice - once on cycle day 4-7 after starting the pill and again at the Lupron evaluation visit, however it is unclear. **Control group:** Small cotton swab placed gently into the cervix.
Outcomes	Reported in paper: - Obtained by author correspondence: live birth, clinical pregnancy, multiple pregnancy, miscarriage
Notes	Trial registration: NCT01800513 (registered Feb 2013, unclear if registered prospectively as recruitment period unclear) Additional concerns and comments: none Funding: NIH and Shady Grove (author correspondence) Author correspondence: yes, undertaken with staff from Shady Grove Publication: unpublished. Investigators provided the individual outcome data on the 19 women randomised. The majority of information was obtained from the trial registration website and verified with the investigators, and protocol and other documents provided by the authors.

Wolff 2018 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors confirmed they used a random number generator
Allocation concealment (selection bias)	High risk	It appears the authors used an open list of trial allocations, the lead investigator was contacted to open a spreadsheet and reveal the next allocation when a new participant was randomised
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Sham procedure involved placement of cotton wool bud inside cervix
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only reporting objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition
Selective reporting (reporting bias)	Unclear risk	Unclear if registered prospectively or not a recruitment period unclear
Other bias	High risk	Trial was stopped early due to difficulty recruiting (target was 254), however this is not considered a bias necessarily. However, no study results have been published, and it is possible that additional methodological flaws in the study exist which have not been detected. It is also unclear if the trial was registered prospectively or not.

Xu 2015

Study characteristics	
Methods	RCT, 2 arms, 30 randomised (additional non-randomised control arm not used) Setting: China, hospital/academic setting, one centre Recruitment period: July 2012 and July 2013
Participants	**Criteria related to previous IVF failure:** no **Inclusion criteria:** age younger than 40 years,FSH less than 10 IU/L, failure of endometrial thickness to reach 7 mm by regular methods (in a prior cycle); no signs of submucosal uterine myoma, uterine malformations, endometrial polyps, or obvious intrauterine adhesion by transvaginal ultrasound or diagnostic hysteroscopy, and no signs of other diseases, which could have affected endometrial growth; and no contraindications for granulocyte colony-stimulating factor treatment (e.g. chronic neutropenia, sickle cell disease, renal disease and history of malignancy). **Exclusion criteria:** -

Xu 2015 *(Continued)*

Interventions	**Study group:** pipelle procedure and granulocyte colony-stimulating factor instillation prior to ovulation (when dominant follicle of 12 mm seen)**Control group:** granulocyte colony-stimulating factor instillation prior to ovulation (when dominant follicle of 12 mm seen)
Outcomes	Reported in paper: live birth, clinical pregnancy, miscarriage Obtained by author correspondence: -
Notes	Trial registration: does not appear to be registered Additional concerns and comments: two of the authors have had two separate papers retracted previously. One was for duplication with another paper they authored in a different journal (PLOS One 2020), and the second was for plagiarisation of a paper that was written by a different author group in a different journal (Zhao 2015). Funding: None stated Author correspondence: Attempted but unsuccessful (lisayanping@sina.com) Publication: full-text.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Described as randomisation with quote: "a randomized number table"
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Although the description of the procedures suggest the procedure may have blinded participants to their allocation, it is not specifically stated that they were blinded and it is unclear whether participants were informed of their trial allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only objective outcomes reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three participants had cancelled cycles; there was no other attrition
Selective reporting (reporting bias)	High risk	Trial does not appear to be registered, and important outcomes such as multiple pregnancy and adverse events not reported
Other bias	High risk	Trial not registered. Additionally, there are concerns about the retractions made of papers written by these authors on two previous occasions.

Yeung 2014

Study characteristics

Methods	RCT, 2 arms, 300 randomised Setting: Hong Kong, academic/research hospital, one centre

Yeung 2014 *(Continued)*

	Recruitment period: March 2011 to August 2013
Participants	**Criteria relating to previous IVF failure:** no **Inclusion criteria:** women undergoing IVF for tubal; unexplained or male factor subfertility with normal uterine cavity as shown on saline sonography/hysteroscopy done at baseline **Exclusion criteria:** presence of hydrosalpinx, endometrial polyp or fibroid distorting uterine cavity; IVF cycles carried out for preimplantation genetic diagnosis; use of donor gametes
Interventions	**Study group:** endometrial aspiration by pipelle performed on luteinizing hormone +7 in the cycle preceding scheduled IVF treatment **Control group:** no procedure All women underwent either hysteroscopy or saline sonography within the 3 months before their IVF cycle (information upheld by corresponding author during study presentation at ESHRE 2014)
Outcomes	Reported in paper: live birth, clinical pregnancy, miscarriage (reported as miscarriage per chemical pregnancy), multiple pregnancy, pain, bleeding Obtained by author correspondence: -
Notes	Trial registration: HKCTR-1646 non-primary registration (registered Jan 2011, registered prospectively); NCT01977976 (registered Nov 2013, registered retrospectively) Additional concerns and comments: the timelines appear to be implausible. Women were recruited until August 2013, followed to live birth, and then the paper was submitted for publication in April 2014. The authors informed us that when they submitted the paper for publication initially, it included only ongoing pregnancy data. During the revision phase the authors updated the manuscript with the live birth data, the latest of which was born in May 2014 and the paper was accepted in July 2014 - therefore the timelines are not implausible. Funding: Small Project Funding 201309176012 of the Committee on Research and Conference Grants, University of Hong Kong. Author correspondence: limited correspondence undertaken with Dr Yeung in previous update Publication: full-text.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Paper states quote: "Computer-generated randomization list with blocks of 10" was used
Allocation concealment (selection bias)	Low risk	Paper states quote: "sealed envelopes" were opened "by a research nurse not involved in the clinical management of the subjects." Unclear if SNOSE - however envelopes were opened by a third party
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding was employed
Blinding of outcome assessment (detection bias) All outcomes	High risk	The outcome of pain during the procedure and bleeding were self-reported by participants who were not blind to their treatment allocation

Yeung 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	There was imbalance in the number of participants withdrawing from the study (19 in the intervention arm and 6 in the control arm), however this is minimal and did not affect the results
Selective reporting (reporting bias)	Low risk	Trial was registered retrospectively, however all review outcomes reported
Other bias	Low risk	Trial registered prospectively with a non-primary trial register (HKCTR). The authors only realised this registration was not adequate when preparing for manuscript submission at which time they registered the trial retrospectively (NCT). The authors provided the ethics approval letter and therefore we have graded this as low-risk.

Zygula 2016

Study characteristics	
Methods	RCT, 2 arms, 120 randomised Setting: Warsaw Medical University Poland - one centre Recruitment period: not stated
Participants	**Criteria related to previous IVF failure:** yes, previous IVF failure (not defined) **Inclusion criteria:** <40 years old **Exclusion criteria:** -
Interventions	**Study group:** endometrial biopsy 7 days after ovulation in the cycle before the IVF cycle **Control group:** casual care
Outcomes	Reported in paper: Clinical pregnancy Obtained by author correspondence: -
Notes	Trial registration: unclear Additional concerns and comments: none Funding: not stated Author correspondence: attempted but unsuccessful Publication: abstract only

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stated as "randomised" only
Allocation concealment (selection bias)	Unclear risk	No description

Zygula 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding employed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only objective outcomes reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Level of attrition is unclear
Selective reporting (reporting bias)	High risk	Study does not appear to be registered and important outcomes such as live birth and adverse events not reported
Other bias	High risk	Trial published as abstract only with limited detail, and further information not obtained from author correspondence. Trial not registered.

ART: assisted reproductive technology**; BMI:** body mass index**; ESHRE:** European Society of Human Reproduction and Embryology; **FET:** frozen embryo transfer; **FIGO:** International Federation of Gynecology and Obstetrics; **HSG:** hysterosalpingography; **ICSI:** intracytoplasmic sperm injection**; ITT:** intention-to-treat**; IU:** international unit; **IVF:** in vitro fertilisation; **RCT:** randomised controlled trial; **RIF:** recurrent implantation failure**; SD:** standard deviation; **SNOSE:** sequentially numbered, opaque sealed envelopes; **USTV:** ultrasonic transvaginal.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ACTRN12611001222932	Investigators confirmed the study never started recruitment
ACTRN12613001046796	Investigators confirmed the study never started recruitment
Alalfy 2019	The intervention is described as causing 'physical endometrial manipulation' however the description of the intervention is similar to a saline instillation:Quote: " A sterilized metal catheter used in hysterosalpingography (Cohen catheter) was inserted in the cervix to pass across the internal os, then 50 ml of saline mixed with hydrocortisone and 1 gram of ampicillin (after skin sensitivity test to exclude patient sensitivity to ampicillin) was injected slowly and continuously in the uterine cavity over 3 minutes to prevent pain and spasm in the corneal ends of the fallopian tubes. After the injection was finished, the cannula remained for another 3 minutes to allow for distension of the tubes." This is not considered to cause significant endometrial disruption and is the topic of a separate Cochrane Review; therefore we excluded this study. NCT03345251
Chang 2017	Study was not truly randomised
Chawla 2015	Retrospective cohort study
Farzadi 2016	It is not clear whether the study was truly randomised, and it is unclear how many women were randomised. Attempts to contact the investigators were unsuccessful. Appears to be this trial registration: IRCT2013072412146N2
Funabiki 2017	Study was removed following author correspondence when the author team discovered quote: "technical problems in data collection process and the following statistical analysis"
Kumbak 2014	Described as non randomised

Study	Reason for exclusion
Liang 2015	Stated as non randomised in the paper
Matsumoto 2014	Study was not truly randomised
Mehrafza 2010	Only an abstract is available which describes the study as randomised, however the total number of women randomised is unclear, and only an overall pregnancy rate is provided (no outcomes per-arm). Correspondence attempted with authors but unsuccessful.
Najdecki 2020	No mention of randomisation in the abstract, we watched the oral presentation at ESHRE where it was stated that the study was retrospective in design.
NCT01798862	This study was converted to a non-randomised trial due to difficulty in recruitment
NCT01842178	Trial registration states: Withdrawn (Principal investigator retired from the project), and there were no participants recruited
NCT01844453	Investigators confirmed the trial was never initiated
NCT02093442	Study was terminated as the study investigator left the institute, no data are available and therefore the study has been excluded (author correspondence with Wellington Martins)
NCT02180256	Study was terminated as the study investigator left the institute, no data are available and therefore the study has been excluded (author correspondence with Wellington Martins)
NCT02197832	Study was terminated due to difficulty recruiting (as per trial registration website). Correspondence with the author team confirmed less than 15 participants were recruited and no data are available, therefore this trial has been excluded
NCT03157765	Investigators confirmed the study never initiated recruitment
NCT04240860	This study is an RCT comparing autologous intrauterine platelet-rich plasma to endometrial scratching for women with thin endometrium. This does not fit in the comparisons included in this review.
Rigos 2019	Authors confirmed in correspondence this was not an RCT but that patients were allocated to arms based on their preference.
Salehpour 2016	Saline infusion is not considered to meet the criteria for endometrial injury. Additionally, the study appears to be pseudo-randomised quote: "Out of 59 participants 20 women agreed and underwent this procedure and the remaining 39 patients underwent regular IVF"
Yoldemir 2011	Study does not seem to be truly randomised, as women in one group 'consisted of women with the injury performed at least two menstrual cycles ago'. The intervention, a mock embryo transfer, is unlikely to produce any endometrial injury
Zhou 2008	Study seems to be pseudo-randomised; it is unclear whether all women in the intervention group received the intervention. We sought additional information, but we could not get in touch with study authors

ESHRE: European Society of Human Reproduction and Embryology; **IVF:** in vitro fertilisation; **RCT:** randomised controlled trial;

Characteristics of studies awaiting classification *[ordered by study ID]*

Aghajanpour 2017

Methods	RCT
Participants	Women with recurrent implantation failure
Interventions	**Study group:** endometrial sampling performed once in the follicular phase and again in the luteal phase (two procedures) **Control group:** endometrial sampling performed once in the luteal phase (one procedure)
Outcomes	No pregnancy outcomes reported
Notes	Only 20 women recruited in total and outcomes focused on VEG expression; no pregnancy data available NCT02480127 Authors confirmed recruitment is completed but report not yet available, in July 2020 (sama.agha-janpour@yahoo.com)

Deepika 2016

Methods	Prospective randomiSed, double-blinded, proof of concept study was conducted in a tertiary care centre from August 2013 to December 2015 in 304 RIF cases defined as 2 previous failed embryo transfers (fresh or frozen) with transfer of at least four good-quality embryos (grade I)
Participants	147 women less than 37 years who have had two previous IVFs.
Interventions	**Study group 1:** endometrial stimulation (ES) was by Pipelle biopsy on day 4-6 of transfer cycle; n = 49 **Study group 2**: endometrial stimulation (ES) was performed on day 20-22 of previous cycle; n = 49 **Control group**: no endometrial stimulation (ES) in previous 3 cycles; n = 49
Outcomes	Clinical pregnancy
Notes	Trial was not registered. It was not possible to extract review outcomes from the abstract (only P values provided), author correspondence unsuccessful, last attempted 03/07/2020.

Hebeihsa 2018

Methods	RCT
Participants	Women undergoing ICSI
Interventions	**Study group:** endometrial injury in the mid-luteal phase of the previous cycle using pipelle and hysteroscopy plus injury performed by hysteroscopy grasper **Control group:** no intervention
Outcomes	Clinical pregnancy
Notes	Trial does not appear to be registered

Hebeihsa 2018 *(Continued)*

	Inconsistencies within the paper including the methods stating that 80 women were recruited to each arm and that there were no cycle cancellations or drop-outs, however the pregnancy outcomes are reported in 60 women in each arm. Additionally, exclusions may have occurred in the hysteroscopy group as the paper states quote: "any abnormality was recorded to exclude the case" - it is not clear how many women were therefore excluded. An email was sent to the corresponding author with no reply.

Mahran 2016

Methods	RCT
Participants	218 women undergoing their first IVF cycle (confirmed by author correspondence as not listed as eligibility criteria but stated in title of paper)
Interventions	**Study group:** pipelle performed between days 21-24 of the cycle prior to the IVF cycle **Control group:** no procedure during luteal phase Note: all women underwent hysteroscopy 2-5 days post menstruation in both groups
Outcomes	Live birth, clinical pregnancy, multiple pregnancy, miscarriage, pain, bleeding (paper states no participants had heavy bleeding, while spotting was common - no data provided). Author confirmed numbers of live births and clinical pregnancies as only percentages provided in the paper
Notes	Trial registration: ISRCTN61316186 (registered Jun 2015, registered retrospectively) Individual participant data were provided for this trial as part of a separate review project (PROSPERO 2017 CRD42017079120), in which some of the current authors are also involved. In doing so, the review team identified discrepancies between the raw data and the published manuscript which could not be resolved following correspondence with the authors. We therefore elected to place the study in awaiting classification.

Shawki 2018

Methods	RCT
Participants	Women undergoing first ICSI
Interventions	**Study group:** endometrial scratch was done in luteal phase of the cycle prior to controlled ovarian hyper stimulation using endometrial bunch biopsy forceps through office hysteroscopy using vaginoscopic approach. **Control group:** unclear
Outcomes	Ongoing pregnancy, clinical pregnancy, multiple pregnancy, miscarriage stated as captured but only percentages supplied for the outcome of ongoing pregnancy (not defined).
Notes	Described as quote: "Randomized controlled trial" however methods are described in the present tense e.g. "half will undergo an endometrial scratch" additionally the phrasing makes it unclear whether the study was truly randomised e.g. quote: "There were 150 subjects who were undergoing their first IVF cycle only 80 (53.3%) subjects who had undergo for scratching." Unclear if truly RCT.

Shawki 2018 *(Continued)*

	Note: same authoring team as Youssef 2018; appearing in same conference proceedings.

Singh 2015

Methods	RCT
Participants	Women with >1 previous failed IVF attempts
Interventions	**Study group:** endometrial scratching will be done once from days 14-18 of menstrual cycle within the same IVF cycle. Anterior and posterior walls of endometrium will be scratched gently by a 4-mm disposable Karman's cannula inserted through the cervical os, and endometrial tissue will be sent for genetic analysis. Oral antibiotic ciprofloxacin 500 mg will be given for 5 days after the procedure **Control group:** no intervention. To avoid the possible confounding effect of antibiotic on IVF success, the control group will be administered the same antibiotic
Outcomes	Live birth, miscarriage However, the data appear to be inconsistent as there is a much higher implantation rate in the intervention arm yet a lower live birth rate. It appears the ongoing pregnancies may refer to pregnancies which were ongoing at the end of the trial (i.e. could be counted as a live birth); however this could not be confirmed with the authors.
Notes	Trial registration: CTRI/2014/01/004307 and CTRI/2013/12/004206 (registered Jan 2014 and Dec 2013, registered retrospectively) Limited correspondence undertaken with Neeta Singh (drneetasingh@yahoo.com)

Vidal 2019

Methods	RCT
Participants	Women without recurrent implantation failure receiving donor eggs
Interventions	**Study group:** endometrial scratching by pipelle biopsy in the luteal phase of the menstrual cycle prior to the embryo transfer **Control group:** no procedure
Outcomes	Ongoing pregnancy, clinical pregnancy, multiple pregnancy, miscarriage
Notes	Trial registration: NCT01955356 (registered Oct 2013, registered prospectively) Study is available as interim analyses only, therefore study is pending the publication of the full text. Correspondence undertaken with Carmina Vidal, Carmina.vidal@ivirma.com

Youssef 2018

Methods	RCT
Participants	Unexplained recurrent implantation failure undergoing ICSI

Youssef 2018 *(Continued)*

Interventions	**Study group:** endometrial scratch was done in luteal phase of the cycle prior to controlled ovarian hyper stimulation using endometrial bunch biopsy forceps through office hysteroscopy using vaginoscopic approach. **Control group:** unclear
Outcomes	Live birth, clinical pregnancy, miscarriage
Notes	Presented as an abstract only with limited methodological detail. Described as an RCT quote: "Patients randomized in 2 equal groups using computer generating table". A total of 200 women included however numbers in each arm unclear and pregnancy rates etc provided as percentages only. Therefore, unclear if truly an RCT and data cannot be used as reported. Note: same authoring team as Shawki 2018; appearing in same conference proceedings.

ICSI: intracytoplasmic sperm injection**; IVF:** in vitro fertilisation; **RCT:** randomised controlled trial; **RIF:** recurrent implantation failure.

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR1800015943

Study name	Effect of endometrial scratching on IVF/ICSI-ET outcomes of women with repeated implantation failure: a randomized controlled trial
Methods	RCT
Participants	Women with implantation failure
Interventions	**Intervention**: endometrial scratching **Control**: No procedure
Outcomes	Clinical pregnancy rate; early abortion rate; live birth rate;
Starting date	May 2018
Contact information	Yang Xiaokui: +86 13810017724, xiaokuiyang2012@163.com
Notes	Trial registration status on 1 July 2020: recruiting Author correspondence: attempted, however no response was received

IRCT20110731007165N4

Study name	Comparison of the effect local endometrial injury on implantation and pregnancy rate in follicular versus luteal phases of the menstrual cycle in patients undergoing frozen embryo transfer with a history of at least one IVF failure
Methods	RCT
Participants	Women undergoing frozen embryo transfer with a history of at least one IVF failure
Interventions	**Intervention**: local endometrial injury in the follicular phase **Control**: local endometrial injury in the luteal phase

IRCT20110731007165N4 *(Continued)*

Outcomes	Chemical pregnancy rate (bHCG), implantation rate (ultrasound), ongoing pregnancy rate (12 weeks)
Starting date	Unclear; expected recruitment start date is 23 September 2017
Contact information	Ladan Kashani: +98 21 8828 1866, kashani_ladan@tums.ac.ir Dr.Zahra Parsaeian: +98 21 7771 9922, zparsaiyan6@gmail.com
Notes	Trial registration status on 1 July 2020: recruitment complete Author correspondence: attempted, however no response was received

IRCT201302091141N13

Study name	Evaluating the effect of endometrial local injury in increasing pregnancy rate in patients undergoing ART (IVF/ICSI)
Methods	RCT
Participants	Women with at least one previous implantation failure
Interventions	**Intervention**: pipelle endometrial sampling 19-21th day in the cycle prior to IVF transfer cycle. **Control**: No procedure
Outcomes	Clinical pregnancy, miscarriage,
Starting date	Expected: 3 April 2013
Contact information	Kiandokht Kiani: +98 21 2230 7960, k.kiani@royaninstitute.org
Notes	Trial registration status on 2 July 2020: recruitment complete. Trial registered on 7 March 2013 Author correspondence sent to Ashrafim@royaninstitute.org; k.kiani@royaninstitute.org, however the emails bounced back.

IRCT201604261556N89

Study name	Effect of local endometrial injury in women with one and two failure history in IVF cycle on success rate of embryo implantation and pregnancy
Methods	RCT
Participants	Women with recurrent implantation failure
Interventions	**Intervention**: local endometrial injury (LEI) with standard pipelle biopsy before IVF procedure in luteal phase of menstrual cycle. **Control**: No procedure
Outcomes	Biochemical pregnancy
Starting date	24 December 2016

IRCT201604261556N89 *(Continued)*

Contact information	Shahin Akhondzadeh: +98 21 5541 2222, s.akhond@sina.tums.ac.ir
Notes	Trial registration status on 3 July 2020: recruitment complete. Author correspondence attempted but unsuccessful

IRCT201708081306N9

Study name	Investigating the success rate of hysteroscopy and endometrial scratching for Intravitro fertilization in recurrent implantation failure case
Methods	RCT
Participants	Women with recurrent implantation failure
Interventions	**Intervention**: endometrial scratching in four direction with curet in luteal phase. **Control**: hysteroscope in luteal phase.
Outcomes	Live birth, ongoing pregnancy, clinical pregnancy, multiple pregnancy, miscarriage
Starting date	23 August 2017
Contact information	Ziba Zahiri +98 13 1322 562, drzibazahiri@gums.ac.ir
Notes	Trial registration status on 3 July /2020: recruitment complete Author correspondence attempted but unsuccessful

IRCT20180425039418N8

Study name	Assessment the effect of endometrial scratch on fertility rate in infertile women undergoing IVF
Methods	RCT
Participants	Women undergoing IVF with no history of IVF failure
Interventions	**Intervention**: 18-24 days before endometrial scrape frozen embryo transfer was done. **Control**: no procedure
Outcomes	Clinical pregnancy, abortion
Starting date	Expected: 22 May 2019
Contact information	Marzieh Ghasemi: +98 54 3329 5715, public@zaums.ac.ir
Notes	Trial registration status on 2 July 2020: recruitment complete. Registered 27 October 2019, retrospectively Correspondence attempted public@zaums.ac.ir; mohammad.ghenaat71@gmail.com, however there was no reply.

IRCT20191031045292N1

Study name	Comparing the effect of endometrial scratch with luteal phase versus follicular phase in FET women candidates outcome
Methods	RCT
Participants	Women candidates for the freeze-frozen transfer cycle
Interventions	**Intervention1**: scratched at the beginning of the follicular phase with the onset of estradiol with a pipelle catheter. **Intervention2**: scratched in the mid-lethal phase of the preceding cycle.
Outcomes	Clinical pregnancy
Starting date	Expected: 22 November 2019
Contact information	Shamim Pilehvar: +98 81 3827 7459, sh.pilehvar@umsha.ac.ir
Notes	Trial registration status on 2 July 2020: recruiting. Trial registered on 16 December 2019. Correspondence attempted, however the email bounced back.

ISRCTN09447850

Study name	Pre In vitro fertilisation (IVF) pipelle biopsy following a previous unsuccessful IVF cycle
Methods	RCT
Participants	Women undergoing an IVF cycle with a history of one or more previous unsuccessful IVF cycles despite having good quality embryos transferred.
Interventions	**Intervention**: gentle scratching (biopsy) is to be performed on Day 21 of the cycle preceding IVF **Control**: no procedure
Outcomes	Clinical pregnancy
Starting date	25 April 2012
Contact information	Dr G Srivastava: garima.srivastava@homerton.nhs.uk
Notes	Trial registration status on 9 Februsry 2019: no longer recruiting. We undertook correspondence with authors who reported that the study has completed but that no report is available.

ISRCTN24605402

Study name	Effect of endometrial scratch on repeat implantation failure following in vitro fertilization embryo transfer or frozen embryo transfer
Methods	RCT

ISRCTN24605402 *(Continued)*

Participants	Patients with repeated implantation failure (two or more) undergoing in vitro fertilisation embryo transfer (IVF-ET) or frozen embryo transfer (FET)
Interventions	**Intervention**: endometrial scratch was offered on day of observation of Luteinizing hormone (LH) + 7 immediately prior to commencement of IVF treatment **Control**: no procedure
Outcomes	Clinical pregnancy
Starting date	16 January 2013
Contact information	Prof Zhang Songying: zhangsongying @126.com, zhangsongying@zju.edu.cn
Notes	Trial registration status on 3 July 2020: no longer recruiting Author correspondence attempted but unsuccessful

ISRCTN63112626

Study name	Effect of endometrial injury on repeat implantation failure following in vitro fertilisation embryo transfer or frozen embryo transfer: a randomised controlled study
Methods	RCT
Participants	**Inclusion criteria:** patients with repeated implantation failure (3 or more) undergoing in vitro fertilisation embryo transfer (IVF-ET) or frozen embryo transfer (FET); patients with normal preoperative routine checks; patients ≤ 40 years of age with basal follicle-stimulating hormone (FSH) < 10 IU/L and > 5 follicles in bilateral ovaries; patients without history of uterine cavity operation within 2 months **Exclusion criteria:** patients with hydrosalpinx; patients with history of endometrial adhesion; patients with uterine malformation; patients with acute genital tract inflammation; patients with history of using hormone such as oral contraceptive within 3 months
Interventions	**Intervention:** endometrial scratching on fifth day after ovulation before IVF or FET cycle in study group. No extra administration before IVF or FET cycle in control group **Control:** no intervention
Outcomes	Clinical pregnancy
Starting date	November 2011
Contact information	Prof. Caihong Ma: no contact details provided
Notes	Trial registration status on3 July 2020. No longer recruiting Investigator emailed multiple times, however have not received any reply from the researchers and could not locate any publication

NCT00367367

Study name	Endometrial curettage before embryo transfer

NCT00367367 *(Continued)*

Methods	RCT
Participants	**Inclusion criteria:** women undergoing IVF/ICSI **Exclusion criteria:** >35 years
Interventions	**Intervention 1:** hysteroscopy and curettage performed on days 15-17 of menstrual cycle **Intervention 2: h**ysteroscopy and curettage performed on days 19-22 of menstrual cycle **Control:** no procedure
Outcomes	Pregnancy
Starting date	December 2005
Contact information	Amir Weiss: weiss_am@clalit.org.il, Joel Geslevich: yoel_g@clalit.org.il
Notes	Trial registration status on 3 July 2020: unknown Author correspondence attempted with authors but unsuccessful

NCT02153814

Study name	Endometrial injury and in vitro fertilization outcomes
Methods	RCT
Participants	Women undergoing IVF
Interventions	**Intervention**: 3 mm endometrial sampling curette, with three passes made of the endometrium along the length of the fundus **Control**: the endometrial sampling curette will be placed 2 cm to 3 cm into the cervix without entering the uterine cavity The first endometrial scratch procedure or sham procedure will be performed up to two weeks prior to expected menses, and the second endometrial scratch or sham procedure will be performed cycle day 5-11 of the stimulation cycle.
Outcomes	Live birth, pregnancy, miscarriage
Starting date	August 2014
Contact information	Gricelda Mendoza: gricelda.mendoza1@northwestern.edu, erica-marsh@northwestern.edu
Notes	Trial registration status on 3 July 2020: recruiting Author correspondence attempted but unsuccessful

NCT02245750

Study name	Value of routine hysteroscopy prior to IVF/ICSI cycles
Methods	RCT

NCT02245750 *(Continued)*

Participants	Women having IVF
Interventions	**Intervention**: hysteroscopy and endometrial injury prior to the IVF/ICSI cycle **Control**: no procedure
Outcomes	Live birth, clinical pregnancy
Starting date	August 2014
Contact information	Ahmed M Mohammed: 00201110362860, ahmadmarzok85@gmail.com Mostafa F Gomaa: 01226188993, mostafafouadg@gmail.com
Notes	Trial registration status on 3 July 2020: unknown Author correspondence undertaken, and authors confirmed the study has completed but that no publication is available.

NCT02306395

Study name	Endometrial local injury to improve the outcome of embryo transfer
Methods	RCT
Participants	Women with RIF(≥ 2) of embryo transfer
Interventions	**Intervention:** endometrial local injury is carried in the first 3-5 days after menstrual period at the same time of hysteroscopy. **Control:** hysteroscopy only
Outcomes	Live birth, clinical pregnancy
Starting date	December 2014
Contact information	Yi Li, 8613548550909, 51261886@qq.com, Yunhai Chuai: +8618810892004, wangyh85@foxmail.com Aiming Wang: +8618600310258, one_army@sina.com
Notes	Trial registration status on 3 July 2020: unknown Author correspondence attempted but unsuccessful

NCT02409745

Study name	The effectiveness of endometrial injury in IVF
Methods	RCT, cross-over
Participants	Patients undergoing frozen thawed embryo transfer.
Interventions	**Intervention**: endometrial injury in luteal phase (previous menstrual cycle) **Control**: endometrial injury in early follicular phase Stratified by age

NCT02409745 *(Continued)*

Outcomes	Clinical pregnancy
Starting date	February 2015
Contact information	Yingpu Sun: 86-13803841888, syp2008@vip.sina.com Linli Hu: 86-15890619576, hulinli1999@163.com
Notes	Trial registration status on 3 July 2020: unknown Also registered as: ChiCTR-IPC-14005419 Author correspondence undertaken and authors informed that the study has been completed but no report was provided.

NCT02522806

Study name	Endometrial local injury before First IVF: evaluation of pregnancy rate (BEONE)
Methods	RCT
Participants	Women having their first IVF cycle
Interventions	**Intervention**: endometrial biopsy (EB) between D17 and D22 of previous ovarian hyperstimulation cycle. **Control**: no procedure
Outcomes	Live birth, ongoing pregnancy, clinical pregnancy, pain
Starting date	September 2014
Contact information	Anne Genod: anne.genod@chu-st-etienne.fr
Notes	Trial registration status on 3 July 2020: completed Author correspondence attempted but unsuccessful

NCT02752568

Study name	Assisted hatching versus endometrial scratch in recurrent implantation failure
Methods	RCT
Participants	Recurrent implantation failure patients undergoing IVF
Interventions	**Intervention**: mid luteal endometrial scratch using Novak curette under general anaesthesia in the cycle preceding stimulation **Control**: no procedure (third group of assisted hatching not relevant for this review)
Outcomes	Positive pregnancy test

NCT02752568 *(Continued)*

Starting date	May 2016
Contact information	Suzy Abdelaziz: suzyabdelaziz92@gmail.com
Notes	Trial registration status on3 July 2020: unknown Author correspondence attempted but unsuccessful

NCT03220503

Study name	Effect of endometrialiInjury before frozen embryo transfer on pregnancy rate
Methods	RCT
Participants	Women undergoing frozen embryo transfer
Interventions	**Intervention:** endometrial scratching on day 7 of transfer cycle **Control:** no procedure
Outcomes	Clinical pregnancy
Starting date	08 March 2017
Contact information	+201008961189 drysherbiny89@gmail.com
Notes	Trial registration status on3 July 2020: unknown Author correspondence attempted but unsuccessful

NCT03470298

Study name	Retrieval versus mid-luteal endometrial scratching (ES) for intracytoplasmic sperm injection (ICSI)
Methods	RCT
Participants	Women having ICSI
Interventions	**Intervention1**: endometrial scratching just after finishing oocyte pick up **Intervention2**: endometrial scratching one week before starting controlled ovarian hyperstimulation. Endometrial scratching performed by Manual Vacuum Aspiration (MVA) size 5 moved from below upwards with suction, scratching anterior uterine wall then posterior then left lateral uterine wall then right lateral uterine wall and lastly funds.
Outcomes	Live birth, clinical pregnancy
Starting date	1 January 2017
Contact information	None provided
Notes	Trial registration status on 03 July 2020: unknown

NCT03470298 *(Continued)*

No contact information provided, unable to contact research team

ART: assisted reproductive technology**; FET:** frozen embryo transfer;**ICSI:** intracytoplasmic sperm injection**; ; IVF:** in vitro fertilisation; **RCT:** randomised controlled trial; **RIF:** recurrent implantation failure.

DATA AND ANALYSES

Comparison 1. Endometrial injury versus control

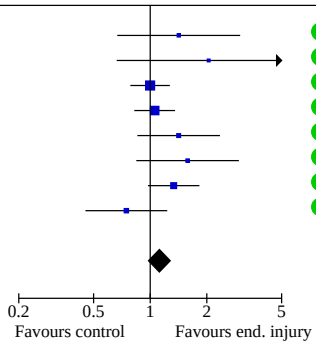
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Live birth per woman randomised (studies at low risk of selection bias and other bias)	8	4402	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.98, 1.28]
1.2 Live birth per woman randomised: sensitivity analysis (no high risk)	1	229	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.63, 2.03]
1.3 Live birth per woman randomised: sensitivity analysis (including all studies)	29		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.4 Live birth per woman randomised: subgrouping by control exposure to endometrial manipulation	8	4402	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.98, 1.28]
1.4.1 No control exposure	8	4402	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.98, 1.28]
1.5 Live birth per woman randomised: subgrouping by RIF	8		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.5.1 Not recurrent or previous implantation failure	6		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.5.2 Recurrent or previous implantation failure	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.5.3 Unselected/unclear number of prior transfers	3		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.6 Live birth per woman randomised: subgrouping by timing of endometrial injury	7	3038	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [1.00, 1.38]
1.6.1 Follicular phase prior cycle	1	229	Odds Ratio (M-H, Fixed, 95% CI)	1.42 [0.67, 3.01]
1.6.2 Luteal phase prior cycle	6	2809	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.99, 1.37]
1.7 Live birth per woman randomised: subgrouping by intensity of endometrial injury	8	4402	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.98, 1.28]

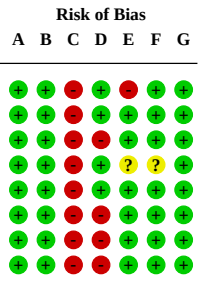
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7.1 Moderate intensity	7	4173	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.97, 1.27]
1.7.2 High intensity	1	229	Odds Ratio (M-H, Fixed, 95% CI)	1.42 [0.67, 3.01]
1.8 Live birth per woman randomised: subgrouping by timing and intensity	7	3038	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [1.00, 1.38]
1.8.1 Follicular phase prior cycle and high intensity	1	229	Odds Ratio (M-H, Fixed, 95% CI)	1.42 [0.67, 3.01]
1.8.2 Luteal phase prior cycle and moderate intensity	6	2809	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.99, 1.37]
1.9 Miscarriage per woman randomised (studies at low risk of selection bias and other bias)	8	4402	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.68, 1.13]
1.10 Miscarriage per woman randomised: sensitivity analysis (no high-risk)	1	229	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.38, 3.58]
1.11 Miscarriage per woman randomised: sensitivity analysis (including all studies)	30	8092	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.85, 1.25]
1.12 Clinical pregnancy per woman randomised (studies at low risk of selection bias and other bias)	8	4402	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.95, 1.23]
1.13 Clinical pregnancy per woman randomised: sensitivity analysis (no high-risk)	1	229	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.67, 2.02]
1.14 Clinical pregnancy per woman randomised: sensitivity analysis (including all studies)	37		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.15 Clinical pregnancy per woman randomised:subgrouping by control exposure to endometrial manipulation	8	4402	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.95, 1.23]
1.15.1 No control exposure	8	4402	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.95, 1.23]
1.16 Clinical pregnancy per woman randomised:subgrouping by RIF	8	4402	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.94, 1.21]
1.16.1 Not recurrent or previous implantation failure	6	3389	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.95, 1.27]
1.16.2 Recurrent or previous implantation failure	2	533	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.63, 1.31]
1.16.3 Unselected/unclear number of prior transfers	3	480	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.66, 1.51]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.17 Clinical pregnancy per woman randomised:subgrouping by timing of endometrial injury	7	3038	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.95, 1.29]
1.17.1 Follicular phase prior cycle	1	229	Odds Ratio (M-H, Fixed, 95% CI)	1.28 [0.62, 2.62]
1.17.2 Luteal phase prior cycle	6	2809	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.94, 1.29]
1.18 Clinical pregnancy per woman randomised:subgrouping by intensity of endometrial injury	8	4402	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.95, 1.23]
1.18.1 Moderate intensity	7	4173	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.94, 1.22]
1.18.2 High intensity	1	229	Odds Ratio (M-H, Fixed, 95% CI)	1.28 [0.62, 2.62]
1.19 Clinical pregnancy per woman randomised:subgrouping by timing and intensity	7	3038	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.95, 1.29]
1.19.1 Follicular phase prior cycle and high intensity	1	229	Odds Ratio (M-H, Fixed, 95% CI)	1.28 [0.62, 2.62]
1.19.2 Luteal phase prior cycle and moderate intensity	6	2809	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.94, 1.29]
1.20 Multiple pregnancy per woman randomised (studies at low risk of selection bias and other bias)	5	3074	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.80, 1.96]
1.21 Multiple pregnancy per woman randomised: sensitivity analysis (no high risk)	1	229	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.24, 4.06]
1.22 Multiple pregnancy per woman randomised: sensitivity analysis (including all studies)	20	5978	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [1.05, 1.68]
1.23 Pain (visual analogue scale): sensitivity analysis (including all studies)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Endometrial injury versus control, Outcome 1: Live birth per woman randomised (studies at low risk of selection bias and other bias)

Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Berntsen 2020	20	122	13	107	2.8%	1.42 [0.67 , 3.01]
Hilton 2019	13	25	9	26	1.0%	2.05 [0.66 , 6.31]
Lensen 2019	180	690	176	674	32.0%	1.00 [0.78 , 1.27]
Metwally 2020	201	523	195	525	29.2%	1.06 [0.82 , 1.36]
Olesen 2019	47	151	37	153	6.2%	1.42 [0.85 , 2.35]
Polanski 2015	40	80	31	80	3.8%	1.58 [0.84 , 2.96]
van Hoogenhuijze 2020	110	472	88	474	16.4%	1.33 [0.97 , 1.83]
Yeung 2014	39	150	48	150	8.6%	0.75 [0.45 , 1.23]
Total (95% CI)		**2213**		**2189**	**100.0%**	**1.12 [0.98 , 1.28]**
Total events:	650		597			



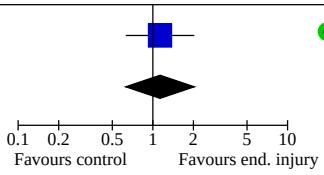


Heterogeneity: Chi² = 8.23, df = 7 (P = 0.31); I² = 15%
Test for overall effect: Z = 1.65 (P = 0.10)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.2. Comparison 1: Endometrial injury versus control, Outcome 2: Live birth per woman randomised: sensitivity analysis (no high risk)

Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Mak 2017 (1)	32	115	29	114	100.0%	1.13 [0.63 , 2.03]
Total (95% CI)		**115**		**114**	**100.0%**	**1.13 [0.63 , 2.03]**
Total events:	32		29			



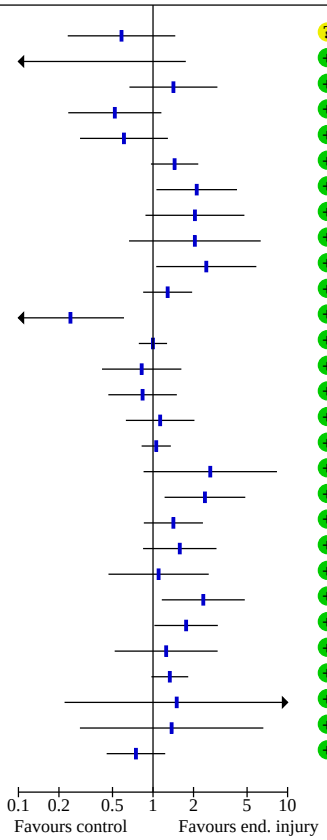
Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)
Test for subgroup differences: Not applicable

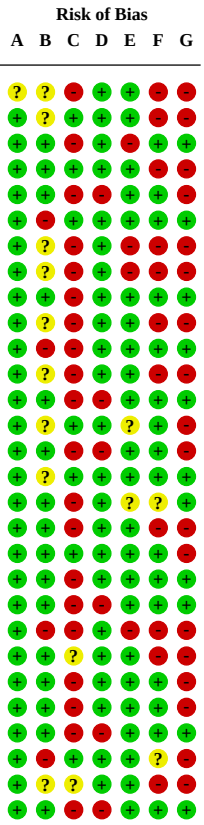
Footnotes
(1) Ongoing pregnancy

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.3. Comparison 1: Endometrial injury versus control, Outcome 3: Live birth per woman randomised: sensitivity analysis (including all studies)

Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Odds Ratio M-H, Fixed, 95% CI
Aflatoonian 2016 (1)	10	50	15	50	0.58 [0.23 , 1.46]
Baum 2012	0	18	4	18	0.09 [0.00 , 1.75]
Berntsen 2020	20	122	13	107	1.42 [0.67 , 3.01]
Eskew 2018	23	53	28	47	0.52 [0.23 , 1.15]
Frantz 2019 (1)	14	98	20	93	0.61 [0.29 , 1.29]
Gibreel 2015	91	193	74	194	1.45 [0.97 , 2.17]
Gurgan 2019	27	153	14	152	2.11 [1.06 , 4.21]
Guven 2014	19	62	11	62	2.05 [0.88 , 4.77]
Hilton 2019	13	25	9	26	2.05 [0.66 , 6.31]
Inal 2012	22	50	12	50	2.49 [1.06 , 5.86]
Izquierdo Rodriguez 2020	96	176	85	176	1.28 [0.85 , 1.95]
Karimzade 2010 (1)	7	77	23	79	0.24 [0.10 , 0.61]
Lensen 2019	180	690	176	674	1.00 [0.78 , 1.27]
Liu 2017 (2)	25	70	29	72	0.82 [0.42 , 1.62]
Mackens 2020	32	100	36	100	0.84 [0.47 , 1.50]
Mak 2017 (1)	32	115	29	114	1.13 [0.63 , 2.03]
Metwally 2020	201	523	195	525	1.06 [0.82 , 1.36]
Narvekar 2010	11	49	5	51	2.66 [0.85 , 8.34]
Nastri 2013	33	79	18	79	2.43 [1.22 , 4.85]
Olesen 2019	47	151	37	153	1.42 [0.85 , 2.35]
Polanski 2015	40	80	31	80	1.58 [0.84 , 2.96]
Shahrokh-Tehraninejad 2016	14	60	13	60	1.10 [0.47 , 2.59]
Shohayeb 2012	28	105	14	105	2.36 [1.16 , 4.81]
Tang 2020	53	110	38	110	1.76 [1.02 , 3.03]
TK 2017	14	55	12	56	1.25 [0.52 , 3.02]
van Hoogenhuijze 2020	110	472	88	474	1.33 [0.97 , 1.83]
Wolff 2018	8	12	4	7	1.50 [0.22 , 10.22]
Xu 2015	5	15	4	15	1.38 [0.29 , 6.60]
Yeung 2014	39	150	48	150	0.75 [0.45 , 1.23]





Footnotes

(1) Ongoing pregnancy

(2) Four arm study condensed into two arms for this analysis

Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

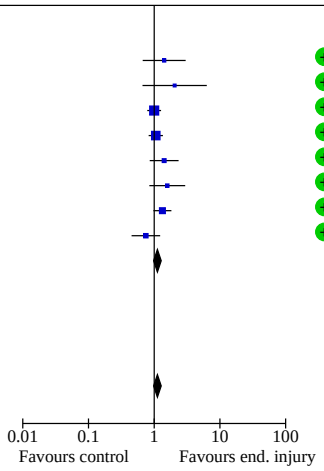
(E) Incomplete outcome data (attrition bias)

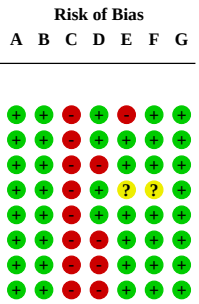
(F) Selective reporting (reporting bias)

(G) Other bias

Analysis 1.4. Comparison 1: Endometrial injury versus control, Outcome 4: Live birth per woman randomised: subgrouping by control exposure to endometrial manipulation

Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.4.1 No control exposure						
Berntsen 2020	20	122	13	107	2.8%	1.42 [0.67 , 3.01]
Hilton 2019	13	25	9	26	1.0%	2.05 [0.66 , 6.31]
Lensen 2019	180	690	176	674	32.0%	1.00 [0.78 , 1.27]
Metwally 2020	201	523	195	525	29.2%	1.06 [0.82 , 1.36]
Olesen 2019	47	151	37	153	6.2%	1.42 [0.85 , 2.35]
Polanski 2015	40	80	31	80	3.8%	1.58 [0.84 , 2.96]
van Hoogenhuijze 2020	110	472	88	474	16.4%	1.33 [0.97 , 1.83]
Yeung 2014	39	150	48	150	8.6%	0.75 [0.45 , 1.23]
Subtotal (95% CI)		**2213**		**2189**	**100.0%**	**1.12 [0.98 , 1.28]**
Total events:	650		597			
Heterogeneity: Chi² = 8.23, df = 7 (P = 0.31); I² = 15%						
Test for overall effect: Z = 1.65 (P = 0.10)						
Total (95% CI)		**2213**		**2189**	**100.0%**	**1.12 [0.98 , 1.28]**
Total events:	650		597			
Heterogeneity: Chi² = 8.23, df = 7 (P = 0.31); I² = 15%						
Test for overall effect: Z = 1.65 (P = 0.10)						
Test for subgroup differences: Not applicable						



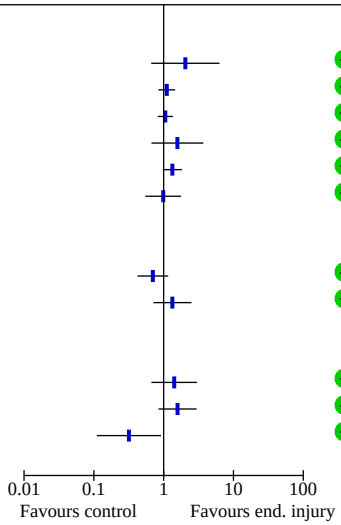


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.5. Comparison 1: Endometrial injury versus control, Outcome 5: Live birth per woman randomised: subgrouping by RIF

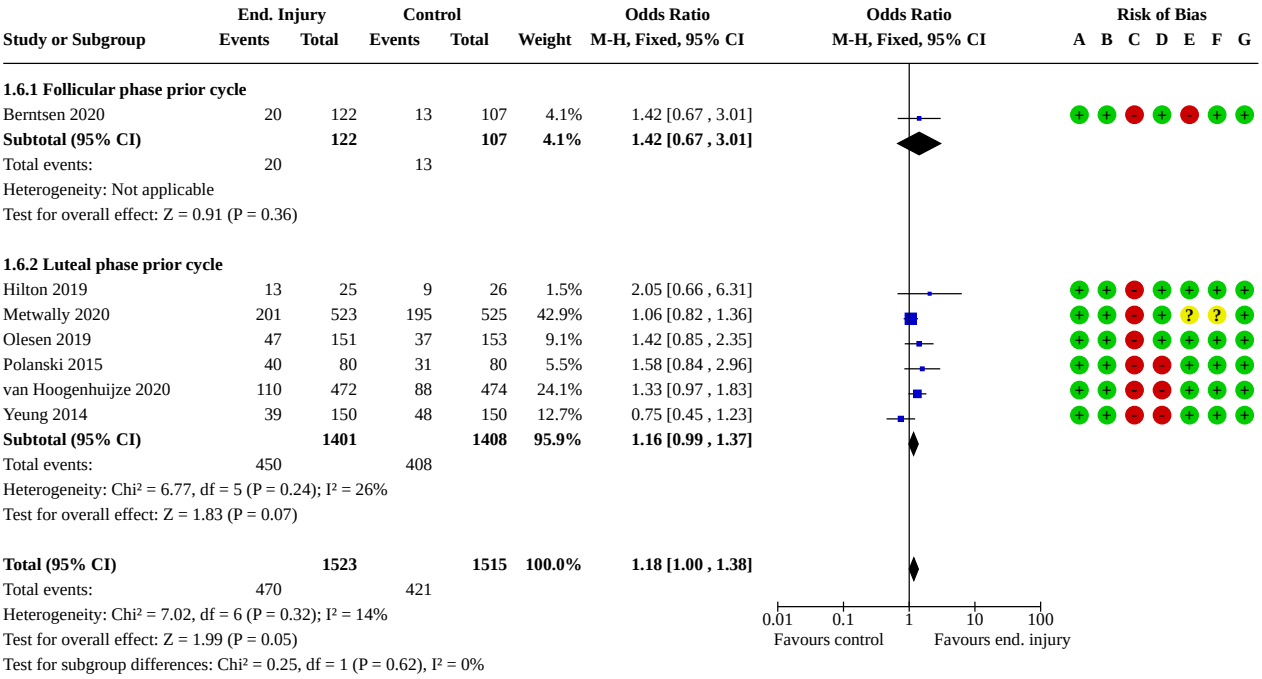
Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F	G
1.5.1 Not recurrent or previous implantation failure												
Hilton 2019	13	25	9	26	2.05 [0.66 , 6.31]	+	+	-	+	+	+	+
Lensen 2019	146	524	130	503	1.11 [0.84 , 1.46]	+	+	-	-	+	+	+
Metwally 2020	201	523	195	525	1.06 [0.82 , 1.36]	+	+	-	+	?	?	+
Olesen 2019	15	47	14	61	1.57 [0.67 , 3.70]	+	+	-	+	+	+	+
van Hoogenhuijze 2020	110	472	88	474	1.33 [0.97 , 1.83]	+	+	-	-	+	+	+
Yeung 2014	32	105	32	104	0.99 [0.55 , 1.78]	+	+	-	-	+	+	+
1.5.2 Recurrent or previous implantation failure												
Lensen 2019	34	166	46	171	0.70 [0.42 , 1.16]	+	+	-	-	+	+	+
Olesen 2019	32	104	23	92	1.33 [0.71 , 2.50]	+	+	-	+	+	+	+
1.5.3 Unselected/unclear number of prior transfers												
Berntsen 2020	20	122	13	107	1.42 [0.67 , 3.01]	+	+	-	+	-	+	+
Polanski 2015	40	80	31	80	1.58 [0.84 , 2.96]	+	+	-	-	+	+	+
Yeung 2014	6	45	15	46	0.32 [0.11 , 0.92]	+	+	-	-	+	+	+



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.6. Comparison 1: Endometrial injury versus control, Outcome 6: Live birth per woman randomised: subgrouping by timing of endometrial injury

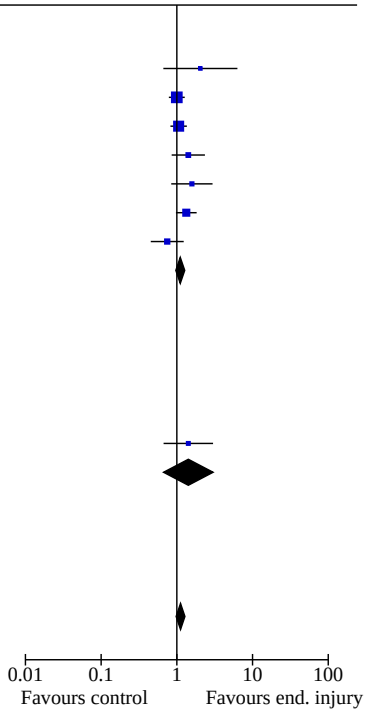


Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
1.6.1 Follicular phase prior cycle							
Berntsen 2020	20	122	13	107	4.1%	1.42 [0.67 , 3.01]	+ + - + - + +
Subtotal (95% CI)		**122**		**107**	**4.1%**	**1.42 [0.67 , 3.01]**	
Total events:	20		13				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.91 (P = 0.36)							
1.6.2 Luteal phase prior cycle							
Hilton 2019	13	25	9	26	1.5%	2.05 [0.66 , 6.31]	+ + - + + + +
Metwally 2020	201	523	195	525	42.9%	1.06 [0.82 , 1.36]	+ + - + ? ? +
Olesen 2019	47	151	37	153	9.1%	1.42 [0.85 , 2.35]	+ + - + + + +
Polanski 2015	40	80	31	80	5.5%	1.58 [0.84 , 2.96]	+ + - - + + +
van Hoogenhuijze 2020	110	472	88	474	24.1%	1.33 [0.97 , 1.83]	+ + - - + + +
Yeung 2014	39	150	48	150	12.7%	0.75 [0.45 , 1.23]	+ + - - + + +
Subtotal (95% CI)		**1401**		**1408**	**95.9%**	**1.16 [0.99 , 1.37]**	
Total events:	450		408				
Heterogeneity: Chi² = 6.77, df = 5 (P = 0.24); I² = 26%							
Test for overall effect: Z = 1.83 (P = 0.07)							
Total (95% CI)		**1523**		**1515**	**100.0%**	**1.18 [1.00 , 1.38]**	
Total events:	470		421				
Heterogeneity: Chi² = 7.02, df = 6 (P = 0.32); I² = 14%							
Test for overall effect: Z = 1.99 (P = 0.05)							
Test for subgroup differences: Chi² = 0.25, df = 1 (P = 0.62), I² = 0%							

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

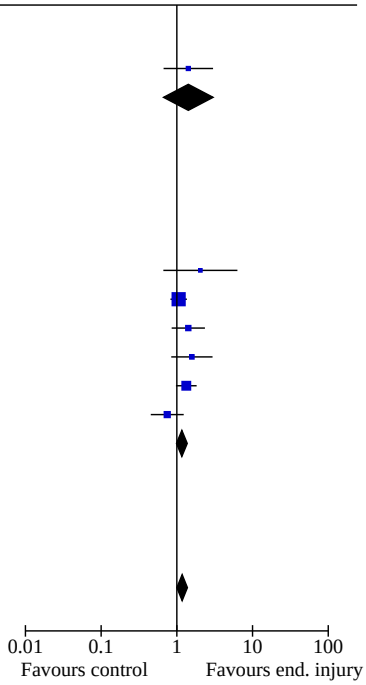
Analysis 1.7. Comparison 1: Endometrial injury versus control, Outcome 7: Live birth per woman randomised: subgrouping by intensity of endometrial injury

Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.7.1 Moderate intensity						
Hilton 2019	13	25	9	26	1.0%	2.05 [0.66 , 6.31]
Lensen 2019	180	690	176	674	32.0%	1.00 [0.78 , 1.27]
Metwally 2020	201	523	195	525	29.2%	1.06 [0.82 , 1.36]
Olesen 2019	47	151	37	153	6.2%	1.42 [0.85 , 2.35]
Polanski 2015	40	80	31	80	3.8%	1.58 [0.84 , 2.96]
van Hoogenhuijze 2020	110	472	88	474	16.4%	1.33 [0.97 , 1.83]
Yeung 2014	39	150	48	150	8.6%	0.75 [0.45 , 1.23]
Subtotal (95% CI)		**2091**		**2082**	**97.2%**	**1.11 [0.97 , 1.27]**
Total events:	630		584			
Heterogeneity: Chi² = 7.84, df = 6 (P = 0.25); I² = 23%						
Test for overall effect: Z = 1.52 (P = 0.13)						
1.7.2 High intensity						
Berntsen 2020	20	122	13	107	2.8%	1.42 [0.67 , 3.01]
Subtotal (95% CI)		**122**		**107**	**2.8%**	**1.42 [0.67 , 3.01]**
Total events:	20		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.91 (P = 0.36)						
Total (95% CI)		**2213**		**2189**	**100.0%**	**1.12 [0.98 , 1.28]**
Total events:	650		597			
Heterogeneity: Chi² = 8.23, df = 7 (P = 0.31); I² = 15%						
Test for overall effect: Z = 1.65 (P = 0.10)						
Test for subgroup differences: Chi² = 0.39, df = 1 (P = 0.53), I² = 0%						



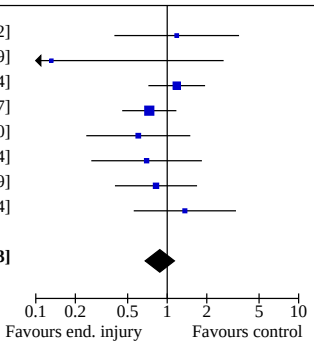
Analysis 1.8. Comparison 1: Endometrial injury versus control, Outcome 8: Live birth per woman randomised: subgrouping by timing and intensity

Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.8.1 Follicular phase prior cycle and high intensity						
Berntsen 2020	20	122	13	107	4.1%	1.42 [0.67 , 3.01]
Subtotal (95% CI)		**122**		**107**	**4.1%**	**1.42 [0.67 , 3.01]**
Total events:	20		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.91 (P = 0.36)						
1.8.2 Luteal phase prior cycle and moderate intensity						
Hilton 2019	13	25	9	26	1.5%	2.05 [0.66 , 6.31]
Metwally 2020	201	523	195	525	42.9%	1.06 [0.82 , 1.36]
Olesen 2019	47	151	37	153	9.1%	1.42 [0.85 , 2.35]
Polanski 2015	40	80	31	80	5.5%	1.58 [0.84 , 2.96]
van Hoogenhuijze 2020	110	472	88	474	24.1%	1.33 [0.97 , 1.83]
Yeung 2014	39	150	48	150	12.7%	0.75 [0.45 , 1.23]
Subtotal (95% CI)		**1401**		**1408**	**95.9%**	**1.16 [0.99 , 1.37]**
Total events:	450		408			
Heterogeneity: Chi² = 6.77, df = 5 (P = 0.24); I² = 26%						
Test for overall effect: Z = 1.83 (P = 0.07)						
Total (95% CI)		**1523**		**1515**	**100.0%**	**1.18 [1.00 , 1.38]**
Total events:	470		421			
Heterogeneity: Chi² = 7.02, df = 6 (P = 0.32); I² = 14%						
Test for overall effect: Z = 1.99 (P = 0.05)						
Test for subgroup differences: Chi² = 0.25, df = 1 (P = 0.62), I² = 0%						



Analysis 1.9. Comparison 1: Endometrial injury versus control, Outcome 9: Miscarriage per woman randomised (studies at low risk of selection bias and other bias)

Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Berntsen 2020	8	122	6	107	4.8%	1.18 [0.40 , 3.52]	+ + - + - + +
Hilton 2019	0	25	3	26	2.7%	0.13 [0.01 , 2.69]	+ + - + + + +
Lensen 2019	36	690	30	674	23.0%	1.18 [0.72 , 1.94]	+ + - - + + +
Metwally 2020	32	523	43	525	32.2%	0.73 [0.45 , 1.17]	+ + - + ? ? +
Olesen 2019	8	151	13	153	9.8%	0.60 [0.24 , 1.50]	+ + - + + + +
Polanski 2015	8	80	11	80	7.9%	0.70 [0.26 , 1.84]	+ + - - + + +
van Hoogenhuijze 2020	14	472	17	474	13.1%	0.82 [0.40 , 1.69]	+ + - - + + +
Yeung 2014	12	150	9	150	6.6%	1.36 [0.56 , 3.34]	+ + - - + + +
Total (95% CI)		**2213**		**2189**	**100.0%**	**0.88 [0.68 , 1.13]**	
Total events:	118		132				
Heterogeneity: Chi² = 5.59, df = 7 (P = 0.59); I² = 0%							
Test for overall effect: Z = 1.00 (P = 0.32)							
Test for subgroup differences: Not applicable							



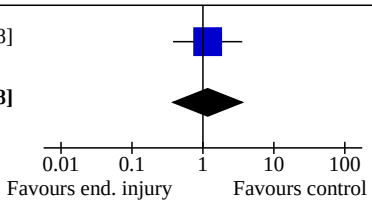
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.10. Comparison 1: Endometrial injury versus control, Outcome 10: Miscarriage per woman randomised: sensitivity analysis (no high-risk)

Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Mak 2017	7	115	6	114	100.0%	1.17 [0.38 , 3.58]
Total (95% CI)		**115**		**114**	**100.0%**	**1.17 [0.38 , 3.58]**
Total events:	7		6			

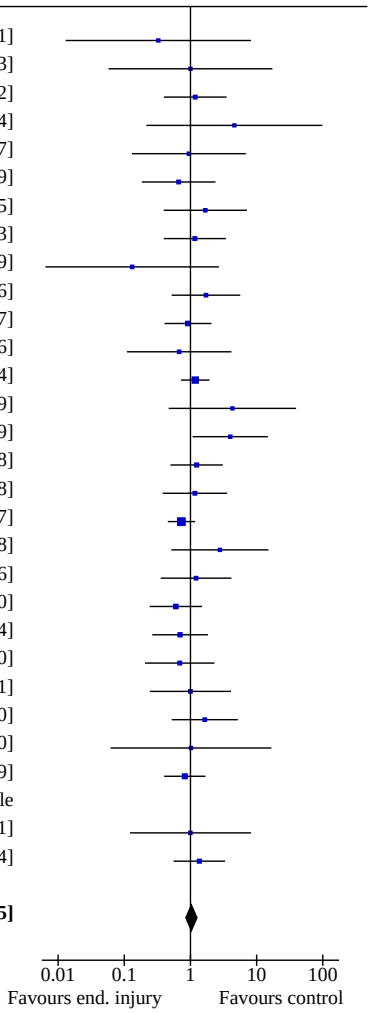
Heterogeneity: Not applicable
Test for overall effect: Z = 0.27 (P = 0.79)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: Endometrial injury versus control, Outcome 11: Miscarriage per woman randomised: sensitivity analysis (including all studies)

Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Aflatoonian 2016 (1)	0	50	1	50	0.7%	0.33 [0.01 , 8.21]
Baum 2012	1	18	1	18	0.5%	1.00 [0.06 , 17.33]
Berntsen 2020	8	122	6	107	2.9%	1.18 [0.40 , 3.52]
Eskew 2018	2	53	0	47	0.2%	4.61 [0.22 , 98.54]
Frantz 2019	2	98	2	93	1.0%	0.95 [0.13 , 6.87]
Gibreel 2015	4	193	6	194	2.8%	0.66 [0.18 , 2.39]
Gurgan 2019	5	153	3	152	1.4%	1.68 [0.39 , 7.15]
Guven 2014	8	62	7	62	3.0%	1.16 [0.39 , 3.43]
Hilton 2019	0	25	3	26	1.6%	0.13 [0.01 , 2.69]
Inal 2012	8	50	5	50	2.0%	1.71 [0.52 , 5.66]
Izquierdo Rodriguez 2020	12	176	13	176	5.9%	0.92 [0.41 , 2.07]
Karimzade 2010	2	77	3	79	1.4%	0.68 [0.11 , 4.16]
Lensen 2019	36	690	30	674	14.0%	1.18 [0.72 , 1.94]
Liu 2017 (2)	4	70	1	72	0.5%	4.30 [0.47 , 39.49]
Mackens 2020	11	100	3	100	1.3%	4.00 [1.08 , 14.79]
Maged 2018	11	150	9	150	4.1%	1.24 [0.50 , 3.08]
Mak 2017	7	115	6	114	2.7%	1.17 [0.38 , 3.58]
Metwally 2020	32	523	43	525	19.6%	0.73 [0.45 , 1.17]
Narvekar 2010	5	49	2	51	0.9%	2.78 [0.51 , 15.08]
Nastri 2013	6	79	5	79	2.2%	1.22 [0.36 , 4.16]
Olesen 2019	8	151	13	153	5.9%	0.60 [0.24 , 1.50]
Polanski 2015	8	80	11	80	4.8%	0.70 [0.26 , 1.84]
Shahrokh-Tehraninejad 2016	5	60	7	60	3.1%	0.69 [0.21 , 2.30]
Shohayeb 2012	4	105	4	105	1.9%	1.00 [0.24 , 4.11]
Tang 2020	8	110	5	110	2.3%	1.65 [0.52 , 5.20]
TK 2017	1	55	1	56	0.5%	1.02 [0.06 , 16.70]
van Hoogenhuijze 2020	14	472	17	474	8.0%	0.82 [0.40 , 1.69]
Wolff 2018	0	12	0	7		Not estimable
Xu 2015	2	15	2	15	0.8%	1.00 [0.12 , 8.21]
Yeung 2014	12	150	9	150	4.0%	1.36 [0.56 , 3.34]
Total (95% CI)		**4063**		**4029**	**100.0%**	**1.03 [0.85 , 1.25]**
Total events:	226		218			

Heterogeneity: Chi² = 18.60, df = 28 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable



Footnotes

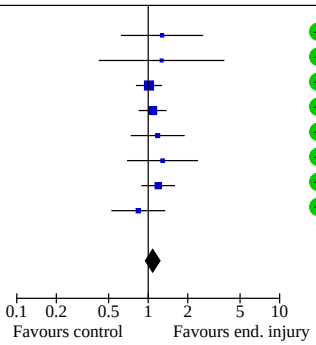
(1) Ongoing pregnancy

(2) Four arm study condensed into two arms for this analysis

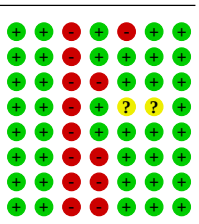
Analysis 1.12. Comparison 1: Endometrial injury versus control, Outcome 12: Clinical pregnancy per woman randomised (studies at low risk of selection bias and other bias)

Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Berntsen 2020	21	122	15	107	2.9%	1.28 [0.62 , 2.62]
Hilton 2019	13	25	12	26	1.2%	1.26 [0.42 , 3.80]
Lensen 2019	217	690	210	674	32.0%	1.01 [0.81 , 1.27]
Metwally 2020	222	523	213	525	26.9%	1.08 [0.84 , 1.38]
Olesen 2019	55	151	50	153	6.9%	1.18 [0.74 , 1.89]
Polanski 2015	45	80	40	80	3.8%	1.29 [0.69 , 2.40]
van Hoogenhuijze 2020	126	472	111	474	17.9%	1.19 [0.89 , 1.60]
Yeung 2014	51	150	57	150	8.3%	0.84 [0.52 , 1.35]
Total (95% CI)		**2213**		**2189**	**100.0%**	**1.08 [0.95 , 1.23]**
Total events:	750		708			

Odds Ratio M-H, Fixed, 95% CI



Risk of Bias



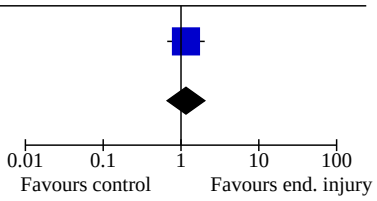
Heterogeneity: Chi² = 2.52, df = 7 (P = 0.93); I² = 0%
Test for overall effect: Z = 1.21 (P = 0.23)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.13. Comparison 1: Endometrial injury versus control, Outcome 13: Clinical pregnancy per woman randomised: sensitivity analysis (no high-risk)

Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Mak 2017	39	115	35	114	100.0%	1.16 [0.67 , 2.02]
Total (95% CI)		**115**		**114**	**100.0%**	**1.16 [0.67 , 2.02]**
Total events:	39		35			

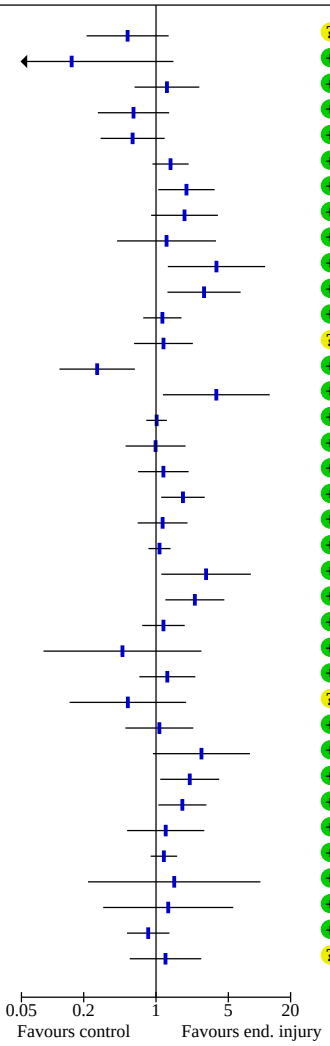
Odds Ratio M-H, Fixed, 95% CI

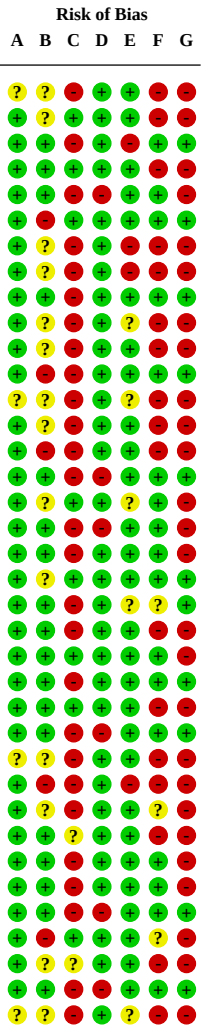


Heterogeneity: Not applicable
Test for overall effect: Z = 0.52 (P = 0.60)
Test for subgroup differences: Not applicable

Analysis 1.14. Comparison 1: Endometrial injury versus control, Outcome 14: Clinical pregnancy per woman randomised: sensitivity analysis (including all studies)

Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Odds Ratio M-H, Fixed, 95% CI
Aflatoonian 2016	10	50	16	50	0.53 [0.21 , 1.32]
Baum 2012	1	18	5	18	0.15 [0.02 , 1.47]
Berntsen 2020	21	122	15	107	1.28 [0.62 , 2.62]
Eskew 2018	25	53	28	47	0.61 [0.27 , 1.34]
Frantz 2019	16	98	23	93	0.59 [0.29 , 1.21]
Gibreel 2015	95	193	80	194	1.38 [0.92 , 2.06]
Gurgan 2019	32	153	18	152	1.97 [1.05 , 3.69]
Guven 2014	27	62	18	62	1.89 [0.90 , 3.97]
Hilton 2019	13	25	12	26	1.26 [0.42 , 3.80]
Hur 2012	19	30	9	29	3.84 [1.30 , 11.32]
Inal 2012	30	50	17	50	2.91 [1.29 , 6.57]
Izquierdo Rodriguez 2020	108	176	102	176	1.15 [0.75 , 1.76]
Karim Zadeh 2008	29	80	26	80	1.18 [0.61 , 2.27]
Karimzade 2010	9	77	26	79	0.27 [0.12 , 0.62]
Karimzadeh 2009	13	58	4	57	3.83 [1.17 , 12.57]
Lensen 2019	217	690	210	674	1.01 [0.81 , 1.27]
Liu 2017 (1)	29	70	30	72	0.99 [0.51 , 1.93]
Mackens 2020	44	100	40	100	1.18 [0.67 , 2.07]
Maged 2018	61	150	41	150	1.82 [1.12 , 2.96]
Mak 2017	39	115	35	114	1.16 [0.67 , 2.02]
Metwally 2020	222	523	213	525	1.08 [0.84 , 1.38]
Narvekar 2010	16	49	7	51	3.05 [1.13 , 8.25]
Nastri 2013	39	79	23	79	2.37 [1.23 , 4.57]
Olesen 2019	55	151	50	153	1.18 [0.74 , 1.89]
Pecorino 2018	2	40	4	40	0.47 [0.08 , 2.75]
Polanski 2015	45	80	40	80	1.29 [0.69 , 2.40]
Safdarian 2011	4	50	7	50	0.53 [0.15 , 1.95]
Shahrokh-Tehraninejad 2016	21	60	20	60	1.08 [0.51 , 2.29]
Sherif 2018	15	30	8	30	2.75 [0.93 , 8.10]
Shohayeb 2012	32	105	18	105	2.12 [1.10 , 4.08]
Tang 2020	64	110	48	110	1.80 [1.05 , 3.07]
TK 2017	15	55	13	56	1.24 [0.53 , 2.93]
van Hoogenhuijze 2020	126	472	111	474	1.19 [0.89 , 1.60]
Wolff 2018	8	12	4	7	1.50 [0.22 , 10.22]
Xu 2015	7	15	6	15	1.31 [0.31 , 5.58]
Yeung 2014	51	150	57	150	0.84 [0.52 , 1.35]
Zygula 2016	18	59	16	61	1.23 [0.56 , 2.74]





Footnotes

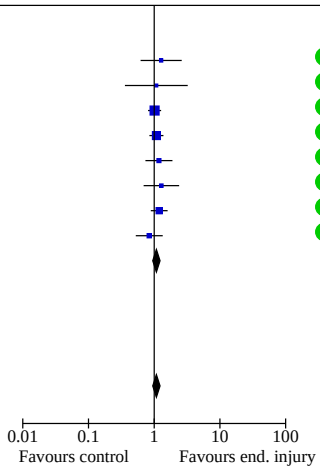
(1) Four arm study condensed into two arms for this analysis

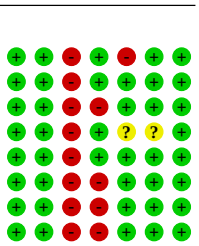
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.15. Comparison 1: Endometrial injury versus control, Outcome 15: Clinical pregnancy per woman randomised:subgrouping by control exposure to endometrial manipulation

Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.15.1 No control exposure						
Berntsen 2020	21	122	15	107	2.9%	1.28 [0.62 , 2.62]
Hilton 2019	12	25	12	26	1.3%	1.08 [0.36 , 3.24]
Lensen 2019	217	690	210	674	32.0%	1.01 [0.81 , 1.27]
Metwally 2020	222	523	213	525	26.9%	1.08 [0.84 , 1.38]
Olesen 2019	55	151	50	153	6.9%	1.18 [0.74 , 1.89]
Polanski 2015	45	80	40	80	3.8%	1.29 [0.69 , 2.40]
van Hoogenhuijze 2020	126	472	111	474	17.8%	1.19 [0.89 , 1.60]
Yeung 2014	51	150	57	150	8.3%	0.84 [0.52 , 1.35]
Subtotal (95% CI)		**2213**		**2189**	**100.0%**	**1.08 [0.95 , 1.23]**
Total events:	749		708			
Heterogeneity: Chi² = 2.44, df = 7 (P = 0.93); I² = 0%						
Test for overall effect: Z = 1.17 (P = 0.24)						
Total (95% CI)		**2213**		**2189**	**100.0%**	**1.08 [0.95 , 1.23]**
Total events:	749		708			
Heterogeneity: Chi² = 2.44, df = 7 (P = 0.93); I² = 0%						
Test for overall effect: Z = 1.17 (P = 0.24)						
Test for subgroup differences: Not applicable						

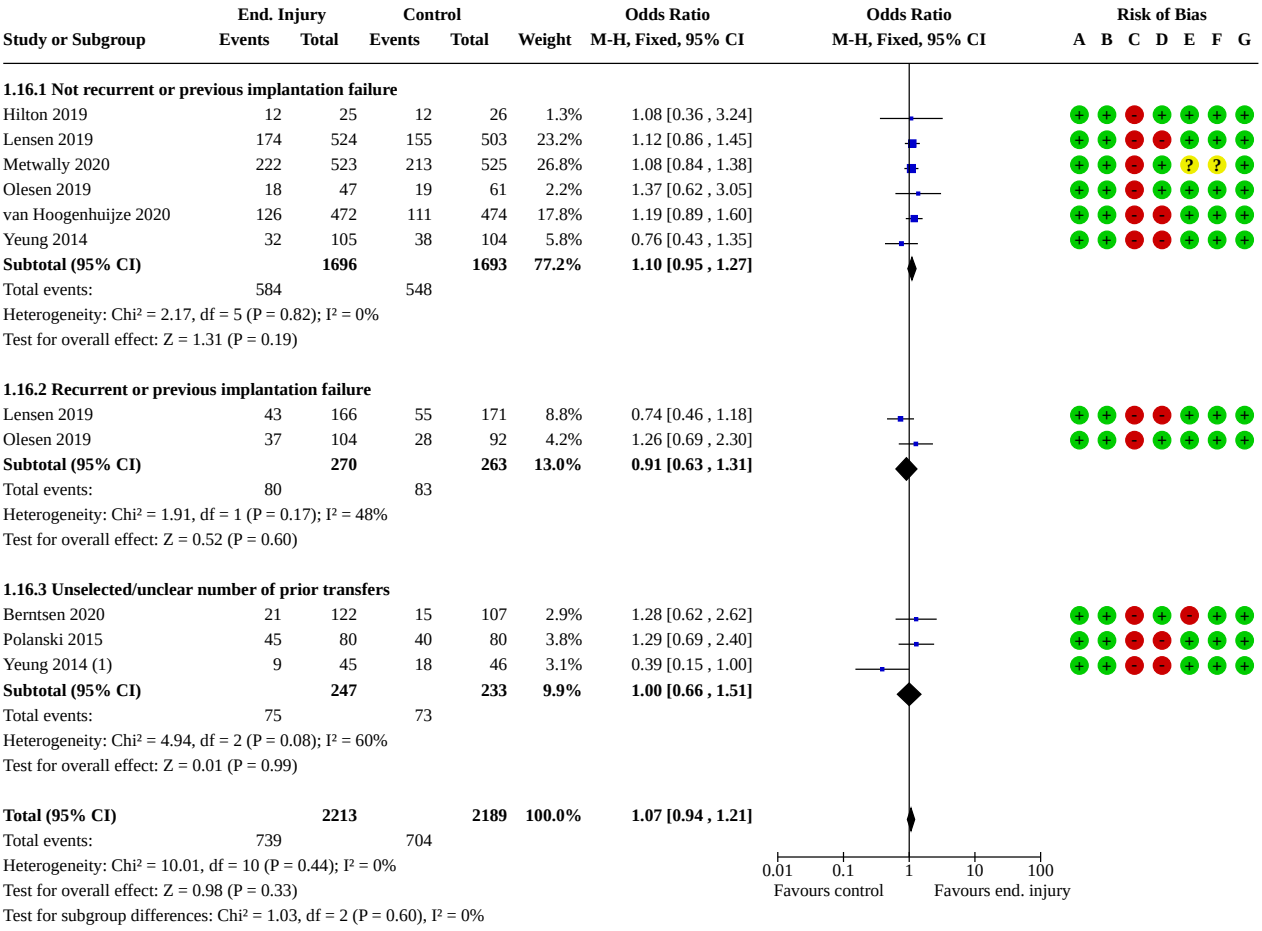




Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.16. Comparison 1: Endometrial injury versus control, Outcome 16: Clinical pregnancy per woman randomised:subgrouping by RIF



Footnotes

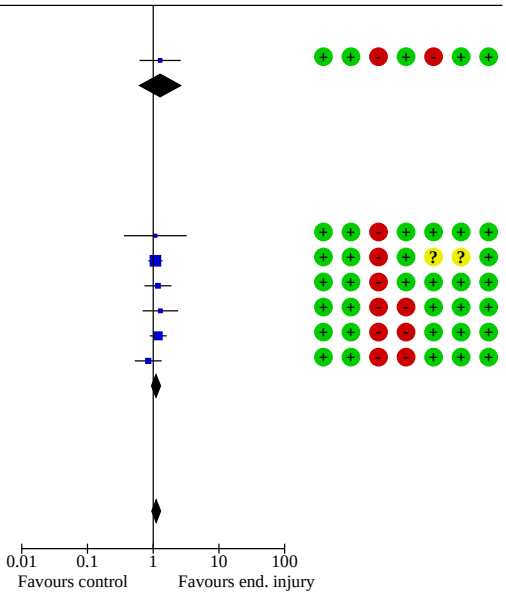
(1) Numbers provided in paper do not sum to the total clinical pregnancy numbers reported

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.17. Comparison 1: Endometrial injury versus control, Outcome 17: Clinical pregnancy per woman randomised:subgrouping by timing of endometrial injury

Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.17.1 Follicular phase prior cycle						
Berntsen 2020	21	122	15	107	4.3%	1.28 [0.62 , 2.62]
Subtotal (95% CI)		**122**		**107**	**4.3%**	**1.28 [0.62 , 2.62]**
Total events:	21		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
1.17.2 Luteal phase prior cycle						
Hilton 2019	12	25	12	26	2.0%	1.08 [0.36 , 3.24]
Metwally 2020	222	523	213	525	39.5%	1.08 [0.84 , 1.38]
Olesen 2019	55	151	50	153	10.2%	1.18 [0.74 , 1.89]
Polanski 2015	45	80	40	80	5.7%	1.29 [0.69 , 2.40]
van Hoogenhuijze 2020	126	472	111	474	26.2%	1.19 [0.89 , 1.60]
Yeung 2014	51	150	57	150	12.2%	0.84 [0.52 , 1.35]
Subtotal (95% CI)		**1401**		**1408**	**95.7%**	**1.10 [0.94 , 1.29]**
Total events:	511		483			
Heterogeneity: Chi² = 1.87, df = 5 (P = 0.87); I² = 0%						
Test for overall effect: Z = 1.22 (P = 0.22)						
Total (95% CI)		**1523**		**1515**	**100.0%**	**1.11 [0.95 , 1.29]**
Total events:	532		498			
Heterogeneity: Chi² = 2.02, df = 6 (P = 0.92); I² = 0%						
Test for overall effect: Z = 1.34 (P = 0.18)						
Test for subgroup differences: Chi² = 0.15, df = 1 (P = 0.70), I² = 0%						

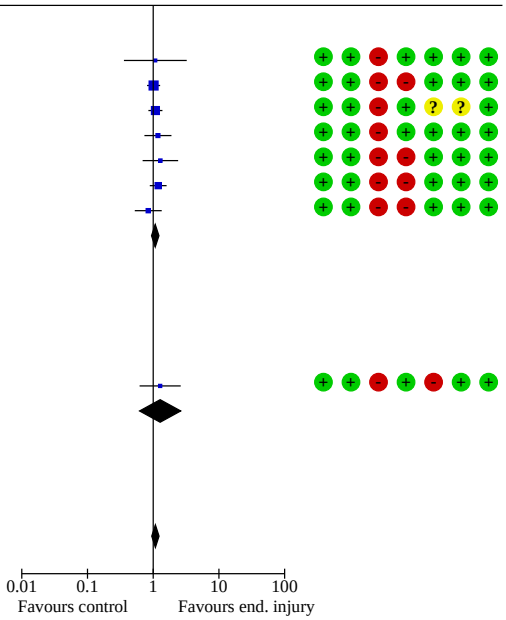


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.18. Comparison 1: Endometrial injury versus control, Outcome 18: Clinical pregnancy per woman randomised:subgrouping by intensity of endometrial injury

Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.18.1 Moderate intensity						
Hilton 2019	12	25	12	26	1.3%	1.08 [0.36 , 3.24]
Lensen 2019	217	690	210	674	32.0%	1.01 [0.81 , 1.27]
Metwally 2020	222	523	213	525	26.9%	1.08 [0.84 , 1.38]
Olesen 2019	55	151	50	153	6.9%	1.18 [0.74 , 1.89]
Polanski 2015	45	80	40	80	3.8%	1.29 [0.69 , 2.40]
van Hoogenhuijze 2020	126	472	111	474	17.8%	1.19 [0.89 , 1.60]
Yeung 2014	51	150	57	150	8.3%	0.84 [0.52 , 1.35]
Subtotal (95% CI)		**2091**		**2082**	**97.1%**	**1.07 [0.94 , 1.22]**
Total events:	728		693			
Heterogeneity: Chi² = 2.23, df = 6 (P = 0.90); I² = 0%						
Test for overall effect: Z = 1.07 (P = 0.28)						
1.18.2 High intensity						
Berntsen 2020	21	122	15	107	2.9%	1.28 [0.62 , 2.62]
Subtotal (95% CI)		**122**		**107**	**2.9%**	**1.28 [0.62 , 2.62]**
Total events:	21		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
Total (95% CI)		**2213**		**2189**	**100.0%**	**1.08 [0.95 , 1.23]**
Total events:	749		708			
Heterogeneity: Chi² = 2.44, df = 7 (P = 0.93); I² = 0%						
Test for overall effect: Z = 1.17 (P = 0.24)						
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.64), I² = 0%						

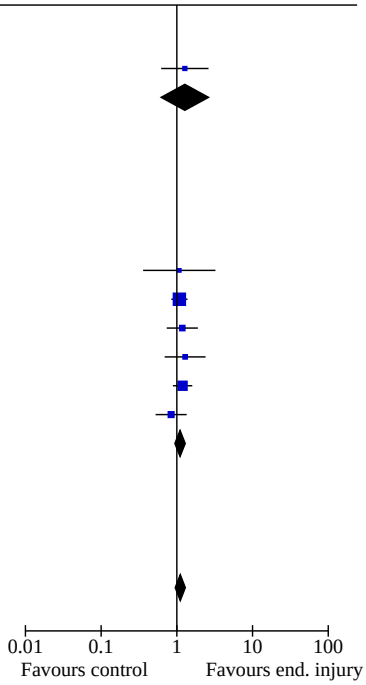


Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

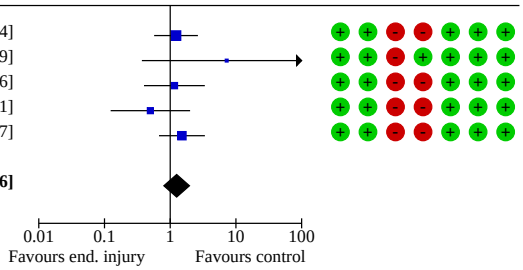
Analysis 1.19. Comparison 1: Endometrial injury versus control, Outcome 19: Clinical pregnancy per woman randomised:subgrouping by timing and intensity

Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.19.1 Follicular phase prior cycle and high intensity						
Berntsen 2020	21	122	15	107	4.3%	1.28 [0.62 , 2.62]
Subtotal (95% CI)		**122**		**107**	**4.3%**	**1.28 [0.62 , 2.62]**
Total events:	21		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
1.19.2 Luteal phase prior cycle and moderate intensity						
Hilton 2019	12	25	12	26	2.0%	1.08 [0.36 , 3.24]
Metwally 2020	222	523	213	525	39.5%	1.08 [0.84 , 1.38]
Olesen 2019	55	151	50	153	10.2%	1.18 [0.74 , 1.89]
Polanski 2015	45	80	40	80	5.7%	1.29 [0.69 , 2.40]
van Hoogenhuijze 2020	126	472	111	474	26.2%	1.19 [0.89 , 1.60]
Yeung 2014	51	150	57	150	12.2%	0.84 [0.52 , 1.35]
Subtotal (95% CI)		**1401**		**1408**	**95.7%**	**1.10 [0.94 , 1.29]**
Total events:	511		483			
Heterogeneity: Chi² = 1.87, df = 5 (P = 0.87); I² = 0%						
Test for overall effect: Z = 1.22 (P = 0.22)						
Total (95% CI)		**1523**		**1515**	**100.0%**	**1.11 [0.95 , 1.29]**
Total events:	532		498			
Heterogeneity: Chi² = 2.02, df = 6 (P = 0.92); I² = 0%						
Test for overall effect: Z = 1.34 (P = 0.18)						
Test for subgroup differences: Chi² = 0.15, df = 1 (P = 0.70), I² = 0%						



Analysis 1.20. Comparison 1: Endometrial injury versus control, Outcome 20: Multiple pregnancy per woman randomised (studies at low risk of selection bias and other bias)

Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Lensen 2019	15	690	12	674	34.5%	1.23 [0.57 , 2.64]
Olesen 2019	3	151	0	153	1.4%	7.24 [0.37 , 141.29]
Polanski 2015	8	80	7	80	18.3%	1.16 [0.40 , 3.36]
van Hoogenhuijze 2020	3	472	6	474	17.3%	0.50 [0.12 , 2.01]
Yeung 2014	16	150	11	150	28.5%	1.51 [0.68 , 3.37]
Total (95% CI)		**1543**		**1531**	**100.0%**	**1.25 [0.80 , 1.96]**
Total events:	45		36			
Heterogeneity: Chi² = 3.25, df = 4 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.99 (P = 0.32)						
Test for subgroup differences: Not applicable						



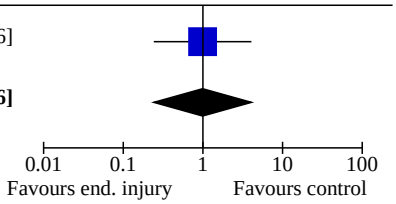
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.21. Comparison 1: Endometrial injury versus control, Outcome 21: Multiple pregnancy per woman randomised: sensitivity analysis (no high risk)

Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Mak 2017	4	115	4	114	100.0%	0.99 [0.24 , 4.06]
Total (95% CI)		**115**		**114**	**100.0%**	**0.99 [0.24 , 4.06]**
Total events:	4		4			

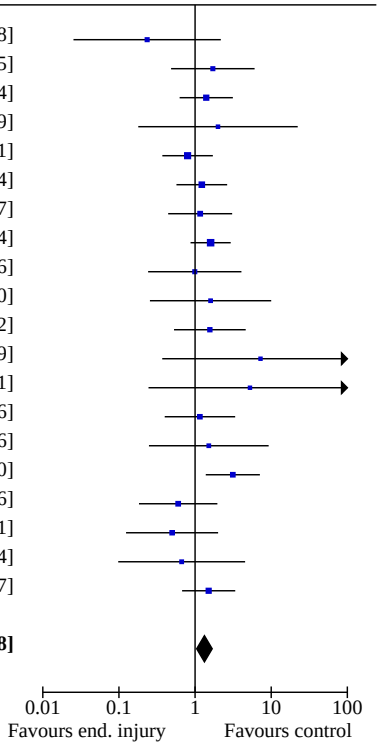
Heterogeneity: Not applicable
Test for overall effect: Z = 0.01 (P = 0.99)
Test for subgroup differences: Not applicable



Analysis 1.22. Comparison 1: Endometrial injury versus control, Outcome 22: Multiple pregnancy per woman randomised: sensitivity analysis (including all studies)

Study or Subgroup	End. Injury Events	End. Injury Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Aflatoonian 2016	1	50	4	50	3.2%	0.23 [0.03 , 2.18]
Frantz 2019	7	98	4	93	3.1%	1.71 [0.48 , 6.05]
Gibreel 2015	15	193	11	194	8.3%	1.40 [0.63 , 3.14]
Gurgan 2019	2	153	1	152	0.8%	2.00 [0.18 , 22.29]
Izquierdo Rodriguez 2020	13	176	16	176	12.1%	0.80 [0.37 , 1.71]
Lensen 2019	15	690	12	674	9.7%	1.23 [0.57 , 2.64]
Liu 2017 (1)	10	70	9	72	6.2%	1.17 [0.44 , 3.07]
Maged 2018	31	150	21	150	13.6%	1.60 [0.87 , 2.94]
Mak 2017	4	115	4	114	3.2%	0.99 [0.24 , 4.06]
Narvekar 2010	3	49	2	51	1.5%	1.60 [0.26 , 10.00]
Nastri 2013	9	79	6	79	4.3%	1.56 [0.53 , 4.62]
Olesen 2019	3	151	0	153	0.4%	7.24 [0.37 , 141.29]
Pecorino 2018	2	40	0	40	0.4%	5.26 [0.24 , 113.11]
Polanski 2015	8	80	7	80	5.1%	1.16 [0.40 , 3.36]
Shohayeb 2012	3	105	2	105	1.6%	1.51 [0.25 , 9.26]
Tang 2020	24	110	9	110	5.7%	3.13 [1.38 , 7.10]
TK 2017	5	55	8	56	5.9%	0.60 [0.18 , 1.96]
van Hoogenhuijze 2020	3	472	6	474	4.9%	0.50 [0.12 , 2.01]
Wolff 2018	4	12	3	7	2.1%	0.67 [0.10 , 4.54]
Yeung 2014	16	150	11	150	8.0%	1.51 [0.68 , 3.37]
Total (95% CI)		**2998**		**2980**	**100.0%**	**1.33 [1.05 , 1.68]**
Total events:	178		136			

Heterogeneity: $Chi^2 = 15.63$, df = 19 (P = 0.68); $I^2 = 0\%$
Test for overall effect: Z = 2.37 (P = 0.02)
Test for subgroup differences: Not applicable

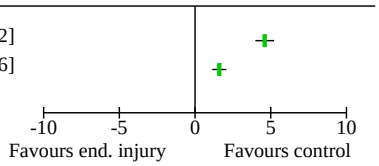


Footnotes

(1) Four arm study condensed into two arms for this analysis

Analysis 1.23. Comparison 1: Endometrial injury versus control, Outcome 23: Pain (visual analogue scale): sensitivity analysis (including all studies)

Study or Subgroup	End. Injury Mean	End. Injury SD	End. Injury Total	Control Mean	Control SD	Control Total	Mean Difference IV, Fixed, 95% CI
Nastri 2013 (1)	6.42	2.35	79	1.82	1.52	79	4.60 [3.98 , 5.22]
Pecorino 2018 (2)	5.6	1.2	40	4	0.9	40	1.60 [1.14 , 2.06]



Footnotes

(1) Sham procedure did not enter the cervix

(2) Sham procedure entered the cervix

Comparison 2. Higher versus lower degree of injury

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Live birth rate per woman randomised: sensitivity analysis (including all studies)	1	129	Odds Ratio (M-H, Fixed, 95% CI)	1.28 [0.31, 5.37]
2.2 Miscarriage: sensitivity analysis (including all studies)	1	129	Odds Ratio (M-H, Fixed, 95% CI)	1.28 [0.31, 5.37]
2.3 Clinical pregnancy per woman randomised: sensitivity analysis (including all studies)	1	129	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [0.46, 3.73]
2.4 Pain (visual analogue scale): sensitivity analysis (including all studies)	1	129	Mean Difference (IV, Fixed, 95% CI)	1.10 [0.29, 1.91]

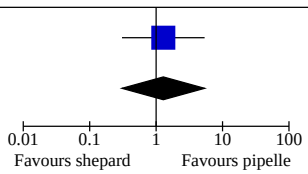
Analysis 2.1. Comparison 2: Higher versus lower degree of injury, Outcome 1: Live birth rate per woman randomised: sensitivity analysis (including all studies)

Study or Subgroup	Pipelle catheter Events	Pipelle catheter Total	Shepard catheter Events	Shepard catheter Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Merriam 2017	4	57	4	72	100.0%	1.28 [0.31 , 5.37]	+ - - - - - -
Total (95% CI)		**57**		**72**	**100.0%**	**1.28 [0.31 , 5.37]**	
Total events:	4		4				

Heterogeneity: Not applicable

Test for overall effect: Z = 0.34 (P = 0.73)

Test for subgroup differences: Not applicable



Risk of bias legend

(A) Random sequence generation (selection bias)

(B) Allocation concealment (selection bias)

(C) Blinding of participants and personnel (performance bias)

(D) Blinding of outcome assessment (detection bias)

(E) Incomplete outcome data (attrition bias)

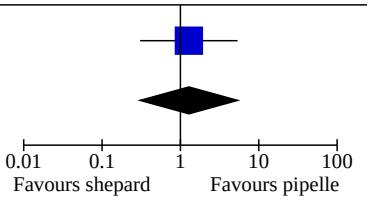
(F) Selective reporting (reporting bias)

(G) Other bias

Analysis 2.2. Comparison 2: Higher versus lower degree of injury, Outcome 2: Miscarriage: sensitivity analysis (including all studies)

Study or Subgroup	Pipelle catheter Events	Total	Shepard catheter Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Merriam 2017	4	57	4	72	100.0%	1.28 [0.31 , 5.37]
Total (95% CI)		**57**		**72**	**100.0%**	**1.28 [0.31 , 5.37]**
Total events:	4		4			

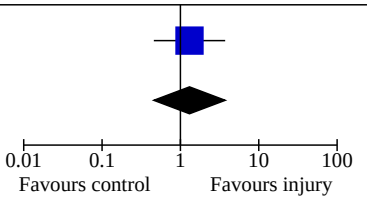
Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.73)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Higher versus lower degree of injury, Outcome 3: Clinical pregnancy per woman randomised: sensitivity analysis (including all studies)

Study or Subgroup	Pipelle catheter Events	Total	Shepard catheter Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Merriam 2017	8	57	8	72	100.0%	1.31 [0.46 , 3.73]
Total (95% CI)		**57**		**72**	**100.0%**	**1.31 [0.46 , 3.73]**
Total events:	8		8			

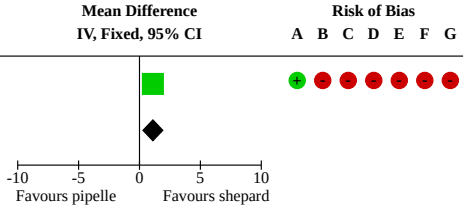
Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.62)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Higher versus lower degree of injury, Outcome 4: Pain (visual analogue scale): sensitivity analysis (including all studies)

Study or Subgroup	Pipelle catheter Mean	SD	Total	Shepard catheter Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Merriam 2017	4.1	2.3	57	3	2.4	72	100.0%	1.10 [0.29 , 1.91]
Total (95% CI)			**57**			**72**	**100.0%**	**1.10 [0.29 , 1.91]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.65 (P = 0.008)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility Group search strategy

ProCite platform

Searched 15 June 2020

Keywords CONTAINS "ART" or "assisted conception" or "assisted reproduction" or "IVF" or "in vitro fertilisation" or "in vitro fertilization" or "intracytoplasmic sperm injection" or "ICSI" or "Intrauterine Insemination" or "IUI" or "artificial insemination" or" *Embryo Transfer" or "ET" or "frozen embryo transfer" or "FET" or "implantation failure" or "recurrent implantation failure" or "subfertility" or Title CONTAINS "ART" or "assisted conception" or "assisted reproduction" or "IVF" or "in vitro fertilisation" or "in vitro fertilization" or "intracytoplasmic sperm injection" or "ICSI" or "Intrauterine Insemination" or "IUI" or "artificial insemination" or"*Embryo Transfer" or "ET" or "frozen embryo transfer" or "FET" or "implantation failure" or "recurrent implantation failure" or "subfertility"

AND

Keywords CONTAINS "endometrial biopsy" or "endometrial injury" or "endometrial trauma" or "mock embryo transfer" or "endometrial sampling" or "endometrial local injury" or "endometrial priming" or "endometrial scratching" or Title CONTAINS "endometrial biopsy" or "endometrial injury" or "endometrial trauma" or "mock embryo transfer" or "endometrial sampling" or "endometrial local injury" or "endometrial priming" or "endometrial scratching"

(168 records)

Appendix 2. CENTRAL via the Cochrane Register of Studies (CRSO) search strategy

Web platform

Searched 15 June 2020

#1 MESH DESCRIPTOR Fertilization in Vitro EXPLODE ALL TREES 2035

#2 MESH DESCRIPTOR Embryo Transfer EXPLODE ALL TREES 1080

#3 MESH DESCRIPTOR Sperm Injections, Intracytoplasmic EXPLODE ALL TREES 530

#4 (embryo transfer*):TI,AB,KY 3677

#5 (in vitro fertili?ation):TI,AB,KY 3362

#6 (ivf or icsi):TI,AB,KY 6430

#7 (intracytoplasmic sperm injection*):TI,AB,KY 1880

#8 (blastocyst* adj2 transfer*):TI,AB,KY 402

#9 (assisted reproducti*):TI,AB,KY 1388

#10 FET:TI,AB,KY 398

#11 (implantation failure*):TI,AB,KY 432

#12 (infertil* or subfertil*):TI,AB,KY 8755

#13 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 13748

#14 (endometri* adj5 injur*):TI,AB,KY 167

#15 (endometri* adj5 traum*):TI,AB,KY 9

#16 (endometri* adj5 biops*):TI,AB,KY 865

#17 (endometri* adj5 harm*):TI,AB,KY 7

#18 (endometri* adj5 damag*):TI,AB,KY 6

#19 (endometri* adj5 inflammation*):TI,AB,KY 23

#20 (endometri* adj5 wound*):TI,AB,KY 102

#21 (endometri* adj5 lesion*):TI,AB,KY 131

#22 (endometri* adj5 scratch*):TI,AB,KY 130

#23 (endometri* adj5 sampl*):TI,AB,KY 298

#24 (mock adj3 transfer*):TI,AB,KY 16

#25 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 1453

#26 #13 AND #25 451

Appendix 3. MEDLINE search strategy

OVID platform

Searched from 1946 to 15 June 2020

1 exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ (41388)
2 embryo transfer$.tw. (12083)
3 in vitro fertili?ation.tw. (23183)
4 ivf-et.tw. (2315)
5 (ivf or et).tw. (287482)
6 icsi.tw. (8422)
7 intracytoplasmic sperm injection$.tw. (7195)
8 (blastocyst adj2 transfer$).tw. (1076)
9 exp reproductive techniques, assisted/ or insemination, artificial/ or exp insemination, artificial, heterologous/ or exp insemination, artificial, homologous/ (69254)
10 artificial insemination.tw. (6620)
11 intrauterine insemination.tw. (2450)
12 assisted reproducti$.tw. (14946)
13 FET.tw. (3266)
14 (subfertil* or infertil*).tw. (64004)
15 implantation failure$.tw. (1613)
16 or/1-15 (398772)
17 (endometri$ adj5 injur$).tw. (267)
18 (endometri$ adj5 trauma$).tw. (109)
19 (endometri$ adj5 biop$).tw. (4940)
20 (endometri$ adj5 harm$).tw. (39)
21 (endometri$ adj5 damag$).tw. (296)
22 (endometri$ adj5 inflammation).tw. (580)
23 (endometri$ adj5 wound$).tw. (244)
24 (endometri$ adj5 lesion$).tw. (3797)
25 (endometri$ adj5 insult$).tw. (7)
26 (endometri$ adj5 scratch$).tw. (87)
27 (endometri$ adj5 sampl$).tw. (3755)
28 (mock adj3 transfer$).tw. (55)
29 or/17-28 (12462)
30 16 and 29 (2327)
31 randomized controlled trial.pt. (507453)
32 controlled clinical trial.pt. (93712)
33 randomized.ab. (482477)
34 placebo.tw. (214171)
35 clinical trials as topic.sh. (191570)
36 randomly.ab. (334996)
37 trial.ti. (219798)
38 (crossover or cross-over or cross over).tw. (84960)
39 or/31-38 (1324553)
40 exp animals/ not humans.sh. (4706900)
41 39 not 40 (1217685)
42 30 and 41 (246)

Appendix 4. Embase search strategy

OVID platform

Searched from 1980 to 15 June 2020

1 exp infertility therapy/ or exp artificial insemination/ or exp embryo disposition/ or exp embryo transfer/ or exp fertilization in vitro/ or exp intracytoplasmic sperm injection/ or exp intrauterine insemination/ or exp oocyte donation/ (99542)

2 exp embryo transfer/ (30917)
3 embryo transfer$.tw. (19407)
4 in vitro fertili?ation.tw. (30256)
5 ivf-et.tw. (3202)
6 (ivf or et).tw. (691827)
7 icsi.tw. (16042)
8 intracytoplasmic sperm injection$.tw. (9604)
9 (blastocyst adj2 transfer$).tw. (2388)
10 artificial insemination.tw. (6089)
11 intrauterine insemination.tw. (3658)
12 assisted reproducti$.tw. (22693)
13 FET.tw. (4626)
14 (subfertil$ or infertil$).tw. (88201)
15 implantation failure$.tw. (3202)
16 or/1-15 (835112)
17 (endometri$ adj5 injur$).tw. (474)
18 (endometri$ adj5 trauma$).tw. (148)
19 (endometri$ adj5 biop$).tw. (7266)
20 (endometri$ adj5 harm$).tw. (75)
21 (endometri$ adj5 damag$).tw. (435)
22 (endometri$ adj5 inflammation).tw. (839)
23 (endometri$ adj5 wound$).tw. (372)
24 (endometri$ adj5 insult$).tw. (9)
25 (endometri$ adj5 lesion$).tw. (5717)
26 (endometri$ adj5 scratch$).tw. (174)
27 (endometri$ adj5 sampl$).tw. (5671)
28 (mock adj3 transfer$).tw. (94)
29 or/17-28 (18385)
30 Clinical Trial/ (965241)
31 Randomized Controlled Trial/ (602685)
32 exp randomization/ (87045)
33 Single Blind Procedure/ (39112)
34 Double Blind Procedure/ (170051)
35 Crossover Procedure/ (63214)
36 Placebo/ (337106)
37 Randomi?ed controlled trial$.tw. (229453)
38 Rct.tw. (37296)
39 random allocation.tw. (2005)
40 randomly allocated.tw. (35133)
41 allocated randomly.tw. (2541)
42 (allocated adj2 random).tw. (815)
43 Single blind$.tw. (24666)
44 Double blind$.tw. (202467)
45 ((treble or triple) adj blind$).tw. (1145)
46 placebo$.tw. (302494)
47 prospective study/ (604945)
48 or/30-47 (2188098)
49 case study/ (69647)
50 case report.tw. (402391)
51 abstract report/ or letter/ (1097252)
52 or/49-51 (1558721)
53 48 not 52 (2134671)
54 16 and 29 and 53 (723)

Appendix 5. PsycINFO search strategy

OVID platform

Searched from 1806 to 15 June 2020

1 exp infertility/ (2158)
2 exp reproductive technology/ (1826)
3 embryo transfer$.tw. (124)

4 in vitro fertili?ation.tw. (749)
5 ivf-et.tw. (19)
6 (ivf or et).tw. (141063)
7 icsi.tw. (72)
8 intracytoplasmic sperm injection$.tw. (56)
9 (blastocyst adj2 transfer$).tw. (4)
10 artificial insemination.tw. (259)
11 intrauterine insemination.tw. (30)
12 assisted reproducti$.tw. (973)
13 FET.tw. (68)
14 implantation failure$.tw. (12)
15 or/1-14 (144633)
16 (endometri$ adj5 injur$).tw. (1)
17 (endometri$ adj5 trauma$).tw. (2)
18 (endometri$ adj5 biop$).tw. (18)
19 (endometri$ adj5 harm$).tw. (1)
20 (endometri$ adj5 damag$).tw. (3)
21 (endometri$ adj5 inflammation).tw. (3)
22 (endometri$ adj5 wound$).tw. (0)
23 (endometri$ adj5 insult$).tw. (0)
24 (endometri$ adj5 lesion$).tw. (18)
25 (mock adj3 transfer$).tw. (0)
26 or/16-25 (46)

Appendix 6. CINAHL search strategy

EBSCO platform

Searched from 1961 to 15 June 2020

#	Query	Results
S39	S24 AND S38	49
S38	S25 OR S26 or S27 or S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37	1,606,041
S37	TX allocat* random*	13,364
S36	(MH "Quantitative Studies")	30,673
S35	(MH "Placebos")	13,740
S34	TX placebo*	71,673
S33	TX random* allocat*	13,364
S32	(MH "Random Assignment")	68,525
S31	TX randomi* control* trial*	222,758
S30	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))	1,221,300
S29	TX ((trebl* n1 blind*) or (trebl* n1 mask*))	294
S28	TX ((trebl* n1 blind*) or (trebl* n1 mask*))	294

(Continued)

S27	TX clinic* n1 trial*	296,110
S26	PT Clinical trial	110,938
S25	(MH "Clinical Trials+")	320,671
S24	S15 AND S23	161
S23	S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22	12,105
S22	TX embryo* N3 transfer*	3,517
S21	TX ovar* N3 hyperstimulat*	979
S20	TX ovari* N3 stimulat*	1,168
S19	TX IVF or TX ICSI	5,780
S18	(MM "Fertilization in Vitro")	3,973
S17	TX vitro fertilization	8,054
S16	TX vitro fertilisation	8,054
S15	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14	2,659
S14	TX endometri* N3 wound*	77
S13	TX endometri* N5 harm*	21
S12	TX endometri* N3 inflammation	69
S11	TX endometri* N3 trauma*	11
S10	TX endometri* N3 damage*	38
S9	TX(endometri* N5 lesion*)	654
S8	TX (endometri* adj5 lesion*)	0
S7	TX (endometri* adj5 lesion*)	0
S6	TX(endometri* N3 insult*)	0
S5	TX (endometri* N5 sampl*)	582
S4	TX mock N3 transfer*	11
S3	TX endometri* N3 scratch*	58
S2	TX endometri* N3 biops*	768
S1	TX endometri* N3 injury	91

Appendix 7. LILACS search strategy

Web platform

Searched 15 June 2020

(tw:(endometri* injury)) OR (tw:(endometri* scratch*)) limited by controlled clinical trial

Appendix 8. Epistemonikos search strategy

Web platform

Searched 15 June 2020

(title:((title:("endometrial scratch*" OR "endometrial injury") OR abstract:("endometrial scratch*" OR "endometrial injury"))) OR abstract:((title:("endometrial scratch*" OR "endometrial injury") OR abstract:("endometrial scratch*" OR "endometrial injury")))) - 16 hits

Appendix 9. DARE Cochrane Database of Systematic Reviews search strategy

OVID platform

Searched from 2005 to November 2012

1. embryo transfer$.tw. (67)
2. in vitro fertili?ation.tw. (104)
3. ivf-et.tw. (17)
4. (ivf or et).tw. (2177)
5. icsi.tw. (74)
6. intracytoplasmic sperm injection$.tw. (55)
7. (blastocyst adj2 transfer$).tw. (15)
8. assisted reproducti$.tw. (90)
9. FET.tw. (18)
10. implantation failure$.tw. (16)
11. or/1-10 (2214)
12. (endometri$ adj5 injur$).tw. (3)
13. (endometri$ adj5 trauma$).tw. (6)
14. (endometri$ adj5 biop$).tw. (34)
15. (endometri$ adj5 harm$).tw. (2)
16. (endometri$ adj5 damag$).tw. (5)
17. (endometri$ adj5 inflammation).tw. (12)
18. (endometri$ adj5 wound$).tw. (20)
19. (endometri$ adj5 lesion$).tw. (17)
20. (endometri$ adj5 insult$).tw. (1)
21. (mock adj3 transfer$).tw. (3)
22. or/12-21 (78)
23. 11 and 22 (34)

WHAT'S NEW

Date	Event	Description
15 June 2020	New citation required and conclusions have changed	The addition of 24 new studies has led to a change in the conclusions of the review.
15 June 2020	New search has been performed	Twenty-four new trials have been included (Aflatoonian 2016; Berntsen 2020; Eskew 2018; Frantz 2019; Gurgan 2019; Hilton 2019; Hur 2012; Izquierdo Rodriguez 2020; Lensen 2019; Liu 2017; Mackens 2020; Maged 2018; Mak 2017; Merriam 2017; Metwally 2020; Olesen 2019; Pecorino 2018; Shahrokh-Tehraninejad 2016; Sherif 2018; Tang 2020; van Hoogenhuijze 2020; Wolff 2018; Xu 2015; Zygula 2016) along with full published versions of two studies that were included as abstracts or unpublished data in

Date	Event	Description
		the previous view (Polanski 2015; TK 2017). The search was updated in February 2019 and again in June 2020.

HISTORY

Protocol first published: Issue 12, 2011
Review first published: Issue 7, 2012

Date	Event	Description
21 January 2015	New citation required and conclusions have changed	Comparisons have been restructured and conclusions have changed
21 January 2015	New search has been performed	9 new studies have been included (Aleyamma 2013; Baum 2012; Gibreel 2015; Guven 2014; Karim Zadeh 2008; Polanski 2014; Safdarian 2011; Shohayeb 2012; Yeung 2014), along with full published versions of 2 studies (Inal 2012; Nastri 2013). We updated the search in January 2015 and categorised 1 study as awaiting classification (Hur 2012a)

CONTRIBUTIONS OF AUTHORS

Updated methods: Sarah F Lensen, Carolina O Nastri, Ahmed Gibreel, Nick Raine-Fenning, Wellington P Martins, Sarah Armstrong

Developed the search strategy: Wellington P Martins, Carolina O Nastri, Ahmed Gibreel

Searched for trials (usually 2 people): Ahmed Gibreel, Sarah F Lensen, Sarah Armstrong, Nick Raine-Fenning

Selected which trials to include (2 + 1 arbiter): Sarah F Lensen, Ahmed Gibreel, Sarah Armstrong

Extracted data from trials (2 + 1 arbiter): Sarah F Lensen, Ahmed Gibreel, Carolina O Nastri, Wellington P Martins, Nick Raine-Fenning

Entered data into RevMan: Sarah F Lensen

Carried out the analysis: Sarah F Lensen

Interpreted the analysis: Carolina O Nastri, Sarah F Lensen, Ahmed Gibreel, Nick Raine-Fenning, Sarah Armstrong, Wellington P Martins

Drafted the final review: Sarah F Lensen

Approved the final version: Carolina O Nastri, Sarah F Lensen, Ahmed Gibreel, Nick Raine-Fenning, Wellington P Martins

DECLARATIONS OF INTEREST

All review authors are investigators or otherwise closely associated with trials included in this review.

Sarah F Lensen is an investigator of one included study (Lensen 2019)

Sarah Armstrong is an investigator of one included study (Lensen 2019)

Ahmed Gibreel is an investigator of one included study (Gibreel 2015)

Carolina O Nastri is an investigator of one included study (Nastri 2013) and two excluded studies (NCT02093442; NCT02180256)

Nick Raine-Fenning is an investigator of one included study (Polanski 2015). He has received lecture payments from GE Healthcare and is a minority share holder in an IVF unit (Nurture)

Wellington P Martins is an investigator of one included study (Nastri 2013) and two excluded studies (NCT02093442; NCT02180256)

SOURCES OF SUPPORT

Internal sources

- Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Brazil

  PhD scholarship
- Faculdade de Medicina de Riberião Preto da Universidade de São Paulo, Brazil

  Author salary

External sources

- None, Other

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have restructured the comparisons in the 2021 update of this review and included post hoc analyses, including a change to the primary analyses.

- In the previous version of the review the comparisons included a timing component, such that trials comparing endometrial injury between day seven of the previous cycle and day seven of the IVF cycle were separated to studies comparing this procedure at other times, namely on the day of oocyte retrieval. For this update of the review, it was decided that the previous day seven categorisation was arbitrary and the effect of the timing of the intervention would be better investigated by subgroup analysis; therefore these comparisons have effectively been merged to create comparison one above.
- After observing substantial risk of bias among the included studies, a post-hoc decision was made to restrict the primary analysis to studies at low risk of selection bias and other bias.

We have changed the method used for data synthesis: The first review was published in 2012 and reported odds ratios under a fixed-effect model. In the 2015 update, the analysis switched to a risk ratio instead of odds ratio under a random-effects model. In this 2021 update we revert back to the original analysis plan and report odds ratios under a fixed-effect model, on the advice of the Cochrane statistical editor.

In previous versions of the review, exposure of the control participants to intentional or inadvertent endometrial disruption was rated as high risk of other bias, due to the potential for this exposure to dilute the observed effect of endometrial injury. However, upon reflection the authors realised that this does not represent a risk of bias per se. Therefore, these bias assessments were changed and the effect of any manipulation in the control group was instead explored in the subgroup analysis.

In the 2015 update the rates of miscarriage and multiple pregnancy were expressed per clinical pregnancy rather than per woman randomised. Following guidance from statistical editors, in the 2021 review we have used the denominator of women randomised to retain the randomised comparison.

INDEX TERMS

Medical Subject Headings (MeSH)

Abortion, Spontaneous [epidemiology] [etiology]; Bias; Embryo Implantation [*physiology]; Endometrium [*injuries]; Fertilization in Vitro [methods]; *Live Birth [epidemiology]; Odds Ratio; Oocyte Retrieval [methods]; Ovulation Induction [methods]; *Pregnancy Rate; Pregnancy, Multiple; Probability; Randomized Controlled Trials as Topic; *Reproductive Techniques, Assisted; Time Factors

MeSH check words

Female; Humans; Pregnancy